Protocol Amendment 6

Study ID: 208887 Master Protocol

Official Title of Study: A Phase I/II, Randomized, Open-label Platform Study Utilizing a Master Protocol to Study Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination With Anti-Cancer Treatments in Participants With Relapsed/Refractory Multiple Myeloma (RRMM) - DREAMM 5

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TITLE PAGE

Protocol Title: A Phase I/II, Randomized, Open-label Platform Study Utilizing a Master Protocol to Study Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Anti-Cancer Treatments in Participants with Relapsed/Refractory Multiple Myeloma (RRMM)–DREAMM5

Protocol Number: 208887 / Amendment 06 for Master Protocol

Compound Number or Name:	Belantamab Mafodotin (GSK2857916)

Study Phase: 1/2

Short Title: Platform Study of Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Anti-Cancer Treatments in Participants with RRMM

Acronym: DREAMM-5

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INVESTIGATOR PROTOCOL AMENDMENT AGREEMENT PAGE

PROTOCOL NUMBER: 208887

AMENDMENT NUMBER: Protocol Amendment 06 for Master Protocol

PROTOCOL TITLE: A Phase I/II, Randomized, Open-label Platform Study Utilizing a Master Protocol to Study Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Anti-Cancer Treatments in Participants with Relapsed/Refractory Multiple Myeloma (RRMM)–DREAMM5

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigator Name:

_____

Investigator Address:

_____

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_____ _____

Investigator Signature Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 6	12 Feb 2024	TMF-15016807
Amendment 5	21 January 2022	TMF-13841939
Amendment 4	14 December 2020	2017N352487_07
Amendment 3	08 July 2020	2017N352487_03
Amendment 2	16 December 2019	2017N352487_02
Amendment 1	24 June 2019	2017N352487_01
Original Protocol	12 March 2019	2017N352487_00

Amendment 06: 12 Feb 2024

Overall Rationale for the Amendment:

The protocol has been amended to make corrections to typographical errors and inconsistencies, to add clarifications in line with program level changes, and to add administrative and safety updates, which are summarized in the table below.

Changes listed in the table below are for the MP only. Changes for Protocol Amendment 6 that are related to specific sub-studies are tabulated at the beginning of each relevant sub-study protocol.

Section # and Name	**Description of Change**	**Brief Rationale**
Throughout document	Changed all instances of Medical Monitor to consistently refer to the Medical Director, and updated medical director contact information	Correction of typographical or consistency error
Throughout document	Updated reference to GSK2857916/ belantamab mafodotin Investigator's Brochure.	To refer to the most recent version of the IB.
Throughout document	Minor editorial and document formatting revisions; applied GSK style guide for abbreviations, date format, etc.	Correction of typographical or consistency errors
Throughout document	The term GSK'916 (used for laboratory samples) was replaced by belantamab mafodotin	Clarification of wording
Throughout document	Updated reference of RAP to SAP	Correction of typographical or consistency errors
Throughout document	Throughout the document and in mTPI table (Table 13) updates made to extend the number of	Clarification of study conduct

Section # and Name	Description of Change	Brief Rationale
	participants in the DE phase to include up to 15 participants.	
Throughout document	Removed specification on how many CEs will be done for each sub-study. The decision of opening a CE is made by iDRC and DEC based on observed data during DE.	Clarification of study conduct
Title page	Update of medical monitor and contact information	Administrative change
Section 1.3 Schedule of Assessments	Removed extraneous text from Table 2 footnote 1	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Table 3, footnote 6, clarified the Hep C RNA testing will be performed to determine participant eligibility if Hep C antibody is positive	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 4, modified footnote 9 for urine and serum immunofixation to include "not quantifiable"	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 4 (footnote 8) and Table 6 (footnote 21), decreased frequency of UPEP assessments	Program level updates
Section 1.3 Schedule of Activities	In Table 4, deleted incorrect footnote associated with calcium corrected for albumin (serum)	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarified guidance regarding realignment of scheduled weekly visits and dosing visits in Table 4	Clarification for study conduct
Section 1.3 Schedule of Assessments	Revision of footnote 4 in Table 4 to clarify that these assessments are not related to dosing	Clarification for study conduct
Section 1.3 Schedule of Activities	Revised language related to imaging for Skeletal surveys in Table 4 footnote 12 and Table 6 footnote 13 and for participants with extramedullary disease in Table 4 footnote 13	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarified that on PK sampling visits, if vital signs assessments are conducted, they should be assessed prior to PK samples being drawn in Table 5, footnote 1	Clarification for study conduct

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Revised to indicate change in timing of EOT to within 30 days from when decision to discontinue treatment in Table 6, footnote 1	Clarification for study conduct
Section 1.3 Schedule of Activities	Updated guidance on pregnancy testing and collection of pregnancy information Table 6, footnote 8	Clarification for study conduct
Section 1.3 Schedule of Assessments	In Table 6, removal of footnote 12 from disease assessments associated with the EOT visit	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Revised to clarify timing of follow-up OSDI questionnaires following the end of treatment in Table 6, footnote 19	Clarification for study conduct
Section 1.3 Schedule of Activities	Corrected the term in the Schedule of Activities to refer to the 'end of treatment' instead of 'end of study' in Table 6, footnote 20	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Update of timing of BM aspirate to occur between C3D1 and C5D1 (predose belantamab mafodotin) from Cycle 1 Day 1 in Table 7	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	In Table 7, clarified that BM aspirate/biopsy collection between C3D1 and C5D1 is predose of belantamab mafodotin	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 7, the term "suspected VGPR, CR/sCR" was corrected to "VGPR or suspected CR/sCR".	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Details regarding FISH testing were removed from Table 7 footnote 3 and reference to Table 31 has been provided.	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 7, created separate rows PD and Suspected PD and added timing of corresponding assessments.	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarified the timing of HBV-DNA testing to allow for grouping with the closest study visit in Table 8	Clarification for study conduct
Section 1.3 Schedule of Assessments	Clarified in Tables 3, 4, and 6 that urine immunofixation should be	Clarification for study conduct

Section # and Name	Description of Change	Brief Rationale
	done on 24 hr urine collection sample	
Section 1.3 Schedule of Activities	In Table 3 and Table 5, clarified that anytime C1D1 Hem/Chem results are outside of eligibility requirements, MD should be contacted prior to dosing. Removed "at Screening" for clarity.	Clarification for study conduct
Section 1.3 Schedule of Assessments, Section 8.2.7 Ophthalmic Assessments	Added ocular exam to Table 4 (footnote 3) and Table 5 (footnote 2), clarified timing of ocular exams in relation to dosing of belantamab mafodotin	Clarification for study conduct
Section 1.3 Schedule of Assessments	Revised footnote text in Table 4 (footnote 4) and Table 5 (footnote 5) to clarify that chemistry panel can be done more frequently as clinically indicated	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 5 footnote 7, removed C18D1 EOI PK sample	Clarification for study conduct
Section 2.3 Benefit/Risk Assessment	Revised risk assessment and aligned with updated risks in belantamab mafodotin Investigator's Brochure Version 11	Program level updates
Synopsis, Section 3 Objectives and Endpoints	Added clarification that the incidence of adverse events of special interest (AESIs) will be collected	Correction of typographical or consistency error
Synopsis, Section 4.1 Overall Design	Revision of language connected with the decision regarding progression from the DE Phase to the CE Phase and clarification that it will be based on the totality of available date	Clarification for study conduct
Section 4.1.1.1 Dose Limiting Toxicities, Table 12	Reorganization of content to improve clarity regarding hematologic toxicities and non-hematologic excluding corneal toxicity	Correction of typographical or consistency error
Section 4.1.1.1 Dose Limiting Toxicities	Added clarification that AEs may be considered as DLT depending on decision of dose escalation meeting	Clarification for study conduct
Section 4.3 Justification for Starting Dose of Belantamab Mafodotin	Corrected the cutoff date for study BMA117159 from June to 26 July 2017	Correction of typographical or consistency error

Section # and Name	Description of Change	Brief Rationale
Section 5 Study Population Section 5.1 Inclusion Criteria for All Participants Section 10 References	Correction of cited reference to Blood. 2011;117(18):4691-4695	Correction of typographical or consistency error
Section 5.1 Inclusion Criteria	Added note that use of legally authorized representative is not applicable for Germany	Alignment with the German Addendum
Section 5.2 Exclusion Criteria	Added reference to 2021 IMWG guidelines for consultation for participants who have had prior or current diagnosis of plasma cell leukemia	Clarification for study conduct
Section 5.4 Screen Failures	Added a reference to Section 1.3 for applicable windows for Screening procedures	Clarification for study conduct.
Section 6.5.1 Permitted Concomitant Medications and Therapies	Added statement regarding the use of monoclonal antibody therapies for the treatment of serious conditions not related to multiple myeloma may be permitted after consultation with the Medical Director	Program level update
Section 6.3 Preparation/Handling/Storage/Accountability	Updated reference from SRM to Pharmacy manual	Correction of typographical or consistency error
Section 6.6.1 Belantamab Mafodotin Dose Adjustments Due to Body Weight	Clarification on calculation of belantamab mafodotin dosage based on body weight	Clarification for study conduct
Section 6.6.4 Belantamab Mafodotin Dose Reductions or Delays	Revised language to refer to safety language as “associated (with)” drug in place of “related (to)”	Correction of typographical or consistency error
Section 6.6.4 Belantamab Mafodotin Dose Reductions or Delays, Table 18	Dose modification guidelines for belantamab mafodotin updated to align with NCI-CTCAE guidelines	Alignment with program level updates
Section 6.6.4 Belantamab Mafodotin Dose Reductions or Delays, Table 19	Clarified definition of severe superficial keratopathy to focus on diffuse microcyst-like deposits that involved the central cornea	Clarification for study conduct
Section 1.3 Schedule of Activities, and Section 8.1 Efficacy Assessments	Clarified that for participants who are discontinuing IP due to PD, the confirmation of laboratory parameters must be performed from a different blood and/or urine collection either on the same day, or preferably within 14 days of the	Correction of typographical or consistency error

Section # and Name	Description of Change	Brief Rationale
	original date of suspected disease progression, and before initiation of any new anti-myeloma therapy	
Section 8 Study Assessments and Procedures	Clarified when a participant was considered enrolled in the study	Program level change
Section 8.2.1 Physical Examinations	Added statement to ensure participant weight is recorded up to 1 decimal point; updates made to the description of a complete physical exam	Clarification for study conduct
Section 8.2.3 Vital Signs	Removed the mention of respiratory rate from the lists of measurements when vital signs are assessed	Clarification for study conduct
Section 8.5.1 Blood Sample Collection for Pharmacokinetics	Added optionally to the blood sample collection for total antibody Added reference to the laboratory manual	Clarification for study conduct
Section 8.5.2 Pharmacokinetic Sample Analysis	Removed reference to the SRM Removed "sBCMA and ADA" sample collection information	Correction of typographical or consistency error
Section 8.7 Immunogenicity Assessments	Removed collection of serum samples from participants who have discontinued study intervention or were withdrawn from the study	Clarification for study conduct
Synopsis, Section 4.1.2 Cohort Expansion Phase, Section 4.3 Justification for Starting Dose of Belantamab Mafodotin, Section 10 References	Revised statement regarding regulatory approval of belantamab mafodotin	Program level update
Section 1.3 Schedule of Activities Tables 6, 7 Section 8.1 Efficacy Assessments	Removed the need for BM aspiration at end of study visit for MRD assessment in Table 6. Clarified conditions for MRD testing at screen and during study. Added a ±1 month window for follow-up MRD testing in Table 7	Clarification for study conduct
Section 7.1 Discontinuation of Study Treatment	Added details related to participant discontinuation of study treatment	Program level update
Section 7.3 Lost to Follow-Up	Added details related to confirming a participant is lost to follow-up	Program level update
Synopsis, Section 1.2 Schema, Section 4.1.2 Cohort Expansion Phase, Section 6.4 Measures to	Revised language concerning randomization to clarify that it is 2-factor will occur between	Clarification for study conduct

Section # and Name	Description of Change	Brief Rationale
Minimize Bias: Randomization and Blinding, Section 9.2 Sample Size Determination	sub-studies and between combination treatment and monotherapy within a sub-study with prior lines of therapy as stratification factor	
Synopsis, Section 4.1 Overall Design, Section 4.1.2 Cohort Expansion Phase, Section 9 Statistical Consideration, Section 9.5.1 Dose Exploration Phase, Section 9.5.2.1 Interim Analysis for Futility	Revised language to clarify how many assessments are required to make a participant evaluable for defined analyses	Clarification for study contact
Section 1.3 Schedule of Activities, Section 12.2	Revised Screening requirement of twice pregnancy testing	Program level update
Section 1.3 Schedule of Assessments; Section 5.2 Exclusion Criteria; Section 6.5.2 Prohibited Concomitant Medications and Non-Drug Therapies; Appendix 2	Added HIV testing at screening to conform with FDA guideline for inclusion of patients previously exposed to HIV. Updated nirogacestat dose modifications when HIV drugs are co-administered.	Program level update
Section 1.3 Schedule of Assessments, Section 8.8 Biomarkers, Section 8.8.2 Cytokine/Chemokine Analysis	Samples for cytokine/chemokines and cryopreserved PBMC analyses will no longer be collected	Update of study conduct
Section 4.1.1.2 mTPI in Dose Exploration, throughout Section 9 Statistical Considerations	Revision of language for clarity and alignment with the SAP	Correction of typographical or consistency error
Section 4.4 Participant Completion and End of Study Definitions	Alignment of language for participant completion of the study and sub-studies and clarified, in the MP, the definition of sub-study completion	Correction of typographical or consistency error
Section 6.6.4 Belantamab Mafodotin Dose Reductions or Delays	Added a footnote to Table 20 to clarify the procedure for restarting belantamab mafodotin after Grade 4 events	Clarification for study conduct
Section 6.6.6 Treatment after the End of the Study	Added text to clarify data collection after EOT while participants are in follow-up	Clarification for study conduct
Section 7.1.3 Infusion-Related Reaction Management and Stopping Criteria, Section 7.1.4 Allergic and Anaphylactic Reaction Stopping Criteria	Clarified that following a Grade 4 IRR or a severe allergic response a participant should permanently discontinue study treatment	Clarification for study conduct

Section # and Name	Description of Change	Brief Rationale
Section 8.3.1.1 Cohort Expansion Belantamab Mafodotin Monotherapy Control Arm	Revision to time period for which SAEs will be assessed	Program level updates
Section 8.8 Biomarkers	Updates to RNA expression studies and addition of section on immune cell phenotyping	Program level updates
Section 8.8.3 Circulating Multiple Myeloma Cells Section 10 References	Added reference to Fernández de Larrea, 2021	Clarification for study conduct
Section 9 Statistical Consideration, Section 9.5.1 Dose Exploration Phase	Revised language related to RP2D of combination therapy for clarity and to state that the goal of the DE Phase is to determine RP2D	Clarification for study conduct
Section 9.2.1 Statistical Operating Characteristics	Changed references to "end of CE" and "final analysis" to "primary analysis"	Clarification for study conduct
Section 9.3 Populations for Analysis	Revised the definition of DLT Evaluable Population to include missed intravenous doses to the criteria used to replace participants who have not received at least 80% of planned doses within Cycle 1	Clarification for study conduct
Section 9.3 Populations for Analysis	In Section 9.3, revised language to clarify that a patient receiving <80% IP due to a non-DLT drug tox would be considered not evaluable	Clarification for study conduct
Section 9.4.2	Updated the likelihood function for the observed data	Clarification for study conduct
Section 9.4.5.2 mTPI Method	Revised language to clarify that decision to escalate may be executed if overdosing interval has the largest UPM	Clarification for study conduct
Section 9.5.2.2. Rolling Safety Evaluation	Revised the number of G4+ events in the combo arm that triggers stopping for safety	Clarification for study conduct
Section 9.6.1 Impact of the Timing When New Sub-Study Starts	Clarification regarding the timing when a new sub-study starts	Clarification for study conduct.
Section 11.1.3 Supplemental Testing for Sub-Studies with Immuno-oncology Agents	In Table 28, changed “plasma cytokine panel” to “serum cytokine panel”	Correction of typographical or consistency error

Section # and Name	Description of Change	Brief Rationale
Section 12.1.3	Added details that personally identifiable information will be collected if there is an unexpected pregnancy for any study participant	Company-level change
Section 12.1.5	Removed section heading Committees Structure	Correction of typographical or consistency error
Section 12.1.9	Clarification of language regarding site and study termination	Clarification for study conduct
Section 12.2 – Appendix 2	Removed Coombs and cytokines/chemokines from Table 31	Clarification for study conduct
Section 12.7.3 Collection of Pregnancy Information	Updated guidance on collection of pregnancy information	Clarification for study conduct
Section 12.12 - Appendix 12	Listing of all third parties and subcontractors who are supporting this study	Program level update

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase I/II, Randomized, Open-label Platform Study Utilizing a Master Protocol to Study Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Anti-Cancer Treatments in Participants with Relapsed/Refractory Multiple Myeloma (RRMM)–DREAMM5

Short Title: Platform Study of Belantamab Mafodotin (GSK2857916) in Combination with Anti-Cancer Treatments in Participants with RRMM

Rationale:

Multiple myeloma (MM) is an incurable malignancy and accounts for 1% of all cancers and for 10% of all hematologic malignancies. Worldwide, approximately 139 000 new cases are diagnosed annually, and an estimated 30 770 new cases and 12 770 deaths will occur in the U.S. in 2018. Despite significant advances, current novel therapies and hematopoietic stem cell transplant (HSCT) cannot achieve cure, and most MM participants will die of disease progression or complications of myeloma. Thus, new treatments are urgently needed.

B-cell maturation antigen (BCMA) is a target present on mature B-cells and on tumor cells in patients with MM. GSK2857916 is an antibody-drug conjugate (ADC) consisting of a humanized anti-BCMA monoclonal antibody (mAb) that is conjugated to the microtubule inhibitor monomethyl auristatin F (MMAF) with a cysteine linker (cys-mcMMAF; also, known as CCI [redacted]). Upon binding to the cell surface, belantamab mafodotin is rapidly internalized and active cytotoxic drug (cys-mcMMAF) is released inside the cell resulting in cell killing through disruption of the microtubule network, leading to cell cycle arrest and apoptosis. Additionally, the antibody is afucosylated, which increases binding to FcγRIIIa receptors and enhances recruitment and activation of immune effector cells, which can kill tumor cells by antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent cellular-mediated phagocytosis (ADCP). Belantamab mafodotin employs distinct mechanisms of action (MoAs) including ADC and antibody-dependent cellular cytotoxicity (ADCC). Moreover, ADC-induced cell death by belantamab mafodotin was recently shown to be immunogenic as measured by cell surface externalization of calreticulin (CRT) and secretion of high mobility group box 1 (HMGB1) and adenosine triphosphate (ATP). Immunogenic cell death (ICD) induced by GSK2857916 resulted in activation of dendritic cells in vitro and is believed to contribute to T cell-mediated anti-tumor responses and durable immunity.

Of the proposed mechanisms of action (MoA) for GSK2857916, the ADC and ADCC MoAs have been linked to efficacy in nonclinical models: in vitro and in vivo against multiple myeloma cell lines, and ex vivo against primary patient myeloma samples. Inhibition of BCMA signaling has been demonstrated biochemically; however, functional effects on myeloma cells have not been demonstrated. ICD markers on cells are induced by belantamab mafodotin both in vivo and in vitro. In vivo, induction of ICD correlates with an adaptive immune response and long-term tumor regression in murine allograft

models. None of the currently approved therapies for MM have the same MoA as belantamab mafodotin. Several assets targeting BCMA by different mechanisms are in clinical development for MM, including BCMA CAR-T cell therapies and anti-BCMA bispecific antibodies.

Despite new medicines in a relapsed refractory population providing clinical benefit, multiple myeloma is not currently curable, and an unmet need remains. Belantamab mafodotin has shown strong single-agent activity in participants with heavily pre-treated RRMM in both the first time in human (FTIH) (BMA117159/DREAMM-1) and the Phase 2 205678/DREAMM-2 studies.

Due to the novel MoA of belantamab mafodotin, it is possible that belantamab mafodotin may be able to overcome resistance to existing therapies.

Overall, in the FTIH BMA117159 and Phase 2 205678 studies, in addition to strong single-agent activity shown in participants with heavily pre-treated RRMM, belantamab mafodotin was well tolerated and adverse events (AEs) were manageable.

Given this previous experience, the combination therapy of belantamab mafodotin with other treatments with different and complementary MoA is an attractive option to explore for participants with MM who have relapsed or become refractory to standard of care (SoC). The combination with other treatments may result in additive, or potentially enhanced effects, which could translate into deep and long-lasting responses.

The platform design is an efficient tool, incorporating a single master protocol (MP), wherein, multiple treatment combinations will be evaluated in separate sub-studies. There will be a dose exploration (DE) Phase which will evaluate the safety and tolerability profile of belantamab mafodotin when administered in combination with other anti-cancer treatments. The number of dose levels explored will vary per sub-study, and up to 15 participants per dose level will be evaluated for safety and preliminary efficacy. One or more potential recommended Phase 2 doses (RP2Ds) for each combination treatment could be identified based on the safety and preliminary efficacy in DE. Where appropriate, These will be followed by a cohort expansion (CE) Phase which will evaluate the clinical activity of the combination treatment in comparison to monotherapy belantamab mafodotin in additional participants with RRMM at each possible RP2D in sub-studies.

The platform design allows for the introduction of new sub-studies, with either a shared control or potentially different control arms, as treatment paradigms evolve. The combination agents for each sub-study of this platform design will be chosen based on scientific rationale and/or available preclinical data. This will lead to generation of robust statistical data in the CE Phase to inform future studies. Detailed information for each sub-study is provided in the respective sub-study protocol sections.

Objectives and Endpoints:

The purpose of this Phase 1/2 study is to determine whether GSK2857916 (belantamab mafodotin) can be safely administered in combination with other anti-cancer treatments that could improve the clinical benefit of belantamab mafodotin in participants with RRMM.

The primary, key secondary, and secondary objectives, along with the corresponding endpoints for DE are listed in Table 1; while the primary, and secondary objectives and endpoints for CE are listed in Table 2.

Table 1 Dose Exploration

Objectives	Endpoints
Primary	
To determine the safety and tolerability of belantamab mafodotin in combination with other anti-cancer treatments (in each sub-study), and to establish the recommended Phase 2 dose for each sub-study investigational combination treatment to explore in the CE Phase in participants with RRMM	• Percentage (number) of participants with dose-limiting toxicities (DLTs) • Percentage of participants with AEs, changes in clinical signs and laboratory parameters
Key Secondary	
To evaluate the clinical measures of efficacy of belantamab mafodotin and combination treatments in each sub-study in participants with RRMM	1. Clinical activity measured as Overall Response Rate (ORR) according to the International Myeloma Working Group (IMWG) Response Criteria
Secondary	
To further evaluate the clinical measures of efficacy of belantamab mafodotin and combination treatments in each sub-study in participants with RRMM	Rates of • Partial Response (PR) • Very Good Partial Response (VGPR) • Complete Response (CR) • Stringent Complete Response (sCR)
To describe the exposure of belantamab mafodotin when administered in combination with each combination treatment within each sub-study in participants with RRMM	• Belantamab mafodotin observed concentrations
To describe the exposure of the partner anti-cancer treatment when administered in combination with belantamab mafodotin in each sub-study	• Anti-cancer combination treatment's observed concentration
To assess anti-drug antibodies (ADAs) against belantamab mafodotin and against combination treatments (biologics) that are administered by IV infusion within each sub-study	• Incidence and titers of ADAs against belantamab mafodotin and combination treatments, when measured
To further determine the safety and tolerability of belantamab mafodotin in combination with other anti-cancer treatments (in each sub-study)	• Incidence of AEs of special interest (AESIs) for belantamab mafodotin • Incidence of AESIs for combination treatments • Incidence of ocular findings on ophthalmic exam

Table 2 Cohort Expansion

Objectives	Endpoints
Primary	
To assess the clinical activity of belantamab mafodotin at each potential RP2D in combination with anti-cancer treatments compared to belantamab mafodotin monotherapy within each sub-study in participants with RRMM	• Overall Response Rate (ORR), according to the International Myeloma Working Group (IMWG) Response Criteria
Secondary	
To further assess clinical activity of combination treatments with belantamab mafodotin within each sub-study at each potential RP2D compared with monotherapy in participants with RRMM	• Clinical Benefit Rate (CBR) according to the IMWG Response Criteria • Progression-Free Survival (PFS) • Duration of Response (DoR) • Time to Response (TTR) • Rates of: Partial Response (PR); Very Good Partial Response (VGPR); Complete Response (CR) stringent Complete Response (sCR) • Overall Survival (OS)
To further characterize the safety of belantamab mafodotin in combination with anti-cancer treatments within each sub-study in participants with RRMM	• Incidence of AEs, Serious Adverse Events (SAEs), AEs leading to discontinuation or dose reduction/delay, changes in clinical signs, and laboratory parameters • Incidence of AESIs for belantamab mafodotin • Incidence of AESIs for the individual partner for each sub-study • Incidence of ocular findings on ophthalmic exam for belantamab mafodotin
To evaluate plasma concentrations of belantamab mafodotin and combination treatments in participants within each sub-study with RRMM	• Belantamab mafodotin and combination treatments' plasma concentrations
To assess anti-drug antibodies (ADAs) against belantamab mafodotin and against combination treatments (biologics) that are administered by IV infusion within each sub-study	• Incidence and titers of ADAs against belantamab mafodotin and combination treatments, when measured

Overall Design:

This is a platform study, which consists of a MP and separate sub-studies. Each sub-study is defined as the data collected in DE and CE for each combination treatment arm and its associated control arm within Study 208887. Information about the combination treatment partner for each sub-study is contained in the respective sub-study protocol section. A sub-study combination treatment will be individually assessed for safety and dose in DE Phase and for safety and efficacy in CE Phase. In CE, each participant will be randomized to combination treatment or the control arm. The control arm will consist of belantamab mafodotin monotherapy.

This is a randomized Phase 1/2, open-label, platform design study of belantamab mafodotin in combination with various anti-cancer combination treatments compared to belantamab mafodotin monotherapy in participants with RRMM. As per the platform design, new sub-studies may be added via future protocol amendment(s) and sub-studies

may be closed by sponsor decision for reasons such as, but not limited to, lack of efficacy and/or undesirable toxicity. Each sub-study investigational treatment combination is evaluated in the DE Phase and, if it passes the interim analysis and progresses, the CE Phase.

As different sub-studies may be added to the platform, at any one time, both DE and CE may be open for different sub-studies. In DE, a participant will be assigned to a sub-study dependent on available treatment slots and eligibility. In CE, participants will be randomized to an available CE sub-study for which they are eligible. Within a CE sub-study, they will be randomized to the combination treatment or the monotherapy control arm. Randomization to combination or monotherapy within a sub-study will be stratified by the number of prior lines of therapy (3-4 vs >4 prior lines). A subset of the sites used in this study will be involved in both DE and CE. Other sites will only be open for CE.

The DE Phase is designed to evaluate safety, tolerability, clinical activity and to select one or more RP2Ds of each sub-study combination treatment. An interim analysis will be performed for each sub-study at the end of DE Phase. A minimum of 2 responders and ≥20% response rate overall as well as acceptable overall safety and other supportive data are needed to move forward into the CE Phase of each sub-study (Figure 1). However, the decision to move to the CE Phase is based on the totality of the data. Dose exploration schemas will be described in the appendix for the respective sub-studies.

CE Phase – Once a combination(s) passes through the DE Phase based on the totality of the data including, but not limited to, safety, PK, and efficacy, participants may be enrolled in the CE Phase of the combination treatment of the sub-study to further assess the clinical benefit and safety of that combination. In the CE Phase, randomization will be utilized to assign participants first to an open CE; and then within a CE to either the investigational or belantamab mafodotin control arm (Figure 1). The dose of belantamab mafodotin used in the control arm will be 2.5 mg/kg Q3W. This is based on results from DREAMM-2. Two interim analyses may be performed for futility evaluation in the CE Phase. Participants are considered evaluable if they have progressed/died, discontinued study treatment, or have had 3 post-baseline efficacy assessments or at least 2 planned doses. Combination therapies will be considered for further development if the posterior probability that ORR with combination treatment is greater than with monotherapy is at least 90%.

Detailed information for each individual combination will be provided in the respective sub-study protocol.

Disclosure Statement:

This is a randomized, open-label Phase 1/2 dose-finding and clinical expansion study utilizing a MP with sub-studies to evaluate belantamab mafodotin in combination with anti-cancer agents in participants with Relapsed/Refractory Multiple Myeloma (RRMM).

Number of Participants:

The study will enroll adult participants with RRMM, who have been previously treated with at least 3 prior lines that include the following: an immunomodulatory drug, proteasome inhibitor (PI) and anti-CD38 treatment (e.g., daratumumab). Lines of therapy are defined by consensus panel of the International Myeloma Workshop (IMWG). Approximately 85 participants per sub-study will be enrolled across the DE and CE Phases of a sub-study. At least 35 participants will be enrolled into belantamab mafodotin monotherapy control group.

Per sub-study the number of participants in each phase is described below:

- **DE Phase:** up to 15 participants per combination treatment dose level in each sub-study. More than 1 dose level will be evaluated.
- **CE Phase:** Once the dose for each combination has been identified, the CE Phase may open for enrolment (multiple CEs may be opened per sub-study, see details in specific sub-studies). Participants in a sub-study at each RP2D will be randomized to either the combination arm in the sub-study (approximately 35 participants) or to the belantamab mafodotin monotherapy shared control arm. Randomization to monotherapy arm may be minimized further depending on when the combination arm starts in the sub-study. Contemporaneous and non-contemporaneous control arm data may be used for the assessment of each combination therapy.
- In this platform study, based on scientific and clinical rationale, more combination treatments (ie, different regimens or new control arms) may be added at any time by protocol amendment.

Treatment Duration:

For each sub-study, refer to the respective sub-study protocol section for further information.

In general, all participants in each sub-study will be treated until disease progression (PD), unless unacceptable toxicity, withdrawal of consent, or death occurs.

Participants who discontinue study treatment for reasons other than confirmed disease progression will enter the Follow-up Period for progression-free survival (PFS) assessment during which they will be followed until disease progression or start of a new anti-myeloma therapy.

Treatment Administration:

Belantamab mafodotin will be administered via intravenous (IV) infusion on day 1 of each cycle until confirmed disease progression, AE leading to study therapy discontinuation, withdrawal of consent or loss to follow-up. Each cycle length may vary per sub-study and will be described in each sub-study appendix.

Data Monitoring Committee: No

GSK Safety Review Team (SRT): Yes

A study specific SRT will be implemented for this study comprised of the GSK study team. The SRT may also meet with investigators on a periodic basis. In line with routine pharmacovigilance, the SRT will review safety data to assess risk:benefit for each sub-study. The remit of the SRT will include, but not be limited to, review of safety data and analysis of risk:benefit for each dosing cohort in the DE Phase, guidance for the transition of each sub-study from dose exploration to cohort expansion and the selection of each RP2D, and ongoing safety monitoring of expansion cohorts. Recommendations on study modification, halting the study and/or pausing enrolment will be provided by the SRT if applicable, as part of its ongoing review of safety data. Membership, roles and accountabilities, and the process for safety review and meeting frequency will be specified in the Dose Escalation Plan.

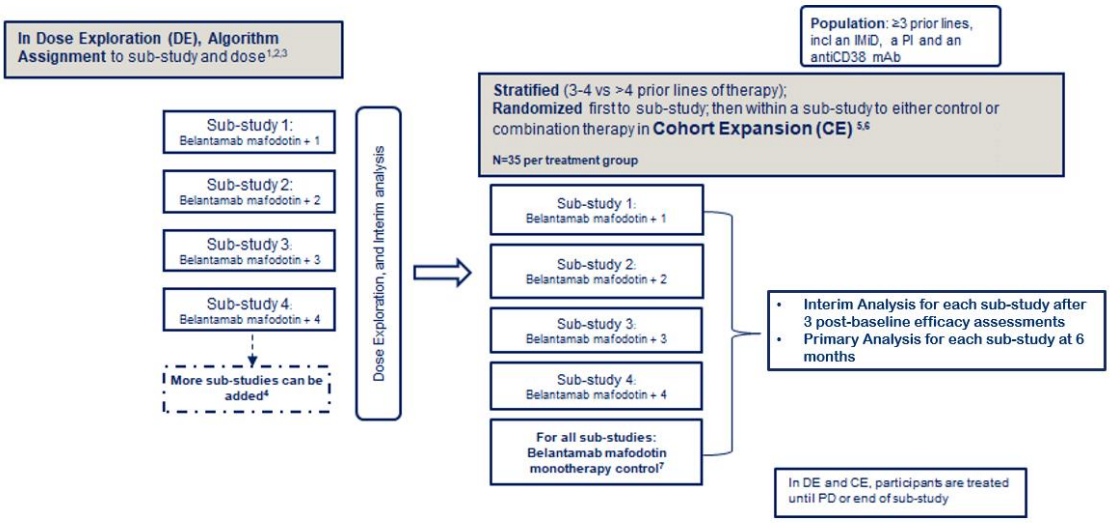
There will be a lead investigator for the entire study. A Steering Committee of the selected investigators on study will also be established to provide guidance for key decisions such as introduction of new arms as well as being available to meet with the SRT or other study team members to discuss any relevant issues as required.

Data Review Committee (DRC): Yes, if requested

In addition to the SRT, a DRC will also be implemented. This committee will be comprised of senior GSK and/or external personnel; however, all members will be external to the GSK208887 study team with relevant areas of expertise, such as clinical and safety. The remit of the DRC will be to support the SRT if requested during the conduct of the study. Details of committee membership, roles and accountabilities, and the process for data review will be specified in the DRC charter.

1.2. Schema

Figure 1 General design myeloma platform study



1. Each sub-study will start with a DE Phase guided by mTPI principles.
2. N per dose level is up to 15.

3. Assignment to sub-study in DE will be according to treatment slot availability. When more than 1 sub-study or dose level is enrolling, allocation will be by predetermined algorithm.
4. Additional sub-studies may be added later by protocol amendment.
5. The number of sub-studies to be investigated and the dose level of combination to be moved forward in CE will be determined from safety, tolerability and interim analyses in DE. Each sub-study in the DE Phase will be evaluated independently and the number of sub-studies moving to CE will not be limited. Please note: The decision to graduate each sub-study from DE to CE will be based on the totality of the data in DE; therefore, some sub-studies may not go forward into CE.
6. Randomization to combination or monotherapy treatment within the CE Phase of a sub-study will be stratified by prior lines of therapy (3-4 vs >4).
7. Control arm may be >35 participants in order to be contemporaneous with enrolling investigational arms.

1.3. Schedule of Activities

The SoA are provided in Table 3, Table 4, Table 5, Table 6, Table 7 below. The following Schedules of Activities applies to all participants in the study. Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. Whenever vital signs and blood draws are scheduled for the same nominal time, vital signs should be performed prior to blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time. Detailed procedures for obtaining each assessment are provided in the SRM.

Response Assessments

For participants who are discontinuing investigational product (IP) due to progressive disease (PD), the confirmation of PD based on laboratory parameters must be performed from a different blood and/or urine collection, either on the same day, or preferably within 14 days of the original date of the suspected disease progression, and before institution of any new anti-myeloma therapy. This may be performed at EOT.

For participants with PD due to extramedullary disease, confirmatory scans are not required. The laboratory parameters do not need to be repeated if the extramedullary disease is the only site of progression.

Imaging for Extramedullary disease

Imaging is only required for participants with extramedullary disease (CT, MRI, or PET/CT can be applied per local guidance). The same modality should be used throughout the study (ie, if CT scan was used as baseline, participant needs to be followed by CT scans). Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For participants with skin only involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the Sum of the Products of the maximal perpendicular diameters of measured lesions.

Imaging of extramedullary disease should be performed every 12 weeks from C1D1, with a window of ±1 week.

If the last radiographic assessment occurred ≥8 weeks prior to the participant's withdrawal from study treatment, and PD has NOT been documented, a new assessment for extramedullary disease should be obtained at EOT. If the participant continues in PFS

follow-up, perform scans for extramedullary disease as clinically indicated. Any additional assessments required for the sub-studies will be documented in the relevant combination partner sections SoAs within respective sub-study protocol section. The timing and number of planned study assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Table 3 SoA – Screening for DE and CE Phases: Belantamab Mafodotin

Screening Study Assessments	Screening	Notes
Note: All Screening assessments must be performed within **30** days prior to Cycle 1 Day 1 (C1D1) unless otherwise specified. Informed Consent must be signed before any study specific assessments are performed. Screening assessments do not need to be repeated at C1D1 unless otherwise specified. All other assessments can be done ≤3 days prior to treatment unless otherwise specified. **If C1D1 Hem/Chem results are outside of the eligibility requirements, Medical Director to be contacted for review prior to dosing**.		
Informed Consent	X	1. Screening/baseline ocular examination will be performed by a qualified eye care specialist (ophthalmologist/optometrist, see Appendix 10) within 30 days prior to C1D1 (see Section 8.2.7 for list of ophthalmic exam procedures). 2. Perform only in WOCBP. A pregnancy test must be performed at Screening. If the test is completed within 72 hours prior to the first dose, this assessment need not be repeated on C1D1. 3. Refer to Appendix 2 for a comprehensive list of lab tests that must be collected for all participants. 4. eGFR as calculated by MDRD formula (Appendix 6). 5. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥1+ at Screening, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void). 6. If a participant tested hepatitis B core antibody positive, refer to Table 8 for additional procedures throughout the study. Hep C RNA testing is optional, but it will be performed to determine participant eligibility if Hep C antibody positive. If negative, participant is eligible (see exclusion criteria 12 for details). 7. Complete at Screening or within 12 weeks prior to C1D1. 8. For participants who have been previously exposed to HIV, HIV viral load must be <400 copies/mL and CD4+ T-cell (CD4+) counts ≥350 cells/uL. 9. Single ECG at Screening. 10. ECHO or MUGA scan for LVEF may be performed within 30 days prior to C1D1. 11. SPEP and UPEP will include M-protein levels. 12. Serum Free Light Chain assay will include kappa/lambda ratio and quantification of involved and uninvolved light chains. 13. IgD/IgE testing is only required for participants with IgD/IgE myeloma. 14. Skeletal survey: Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). X-ray is acceptable for lytic disease, but other methods are needed (CT, MRI, PET/CT) for assessment of extramedullary disease. Skeletal survey results within 30 days prior to C1D1 may be used for Screening. Same modality used at Screening should be used throughout study. 15. In participants with known or suspected extramedullary plasmacytoma, a whole body scan (ie, CT, MRI, or PET-CT) should be performed within 30 days prior to C1D1. The same method should be used throughout the study (ie, if a PET-CT scan was used as baseline scan then the participants need to be
Throughout the study, participants are educated about life style considerations (Section 5.3) for the study and the need for maintaining adequate urinary output (Section 2.3.1)	X	
Inclusion/Exclusion criteria	X	
Past and current medical conditions	X	
Concomitant Medication review	X	
Screening Safety Assessments		
Ocular Exam	X[1]	
ECOG Performance Status	X	
Vital Signs (BP, HR, Body Temperature)	X	
Weight and Height	X	
Serum Pregnancy Test (WOCBP only)	X[2]	
Hematology (CBC)	X[3]	
Clinical chemistry	X[3]	
eGFR	X[4]	
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[5]	
HbsAg, HbcAb[6], HCV[6] tests	X[7]	
HIV viral load and CD4+ count	X[8]	
12-lead ECG	X[9]	
ECHO or MUGA scan for LVEF	X[10]	
Screening Disease Evaluation		
Beta-2 microglobulin	X	
UPEP 24 hr urine collection	X[11]	

Screening Study Assessments	Screening	Notes
Note: All Screening assessments must be performed within **30** days prior to Cycle 1 Day 1 (C1D1) unless otherwise specified. Informed Consent must be signed before any study specific assessments are performed. Screening assessments do not need to be repeated at C1D1 unless otherwise specified. All other assessments can be done ≤3 days prior to treatment unless otherwise specified. **If C1D1 Hem/Chem results are outside of the eligibility requirements, Medical Director to be contacted for review prior to dosing**.		
Urine immunofixation 24 hr urine collection	X	followed by PET-CT scans). Selected target lesions need to be measured and followed over time. Whole body MRI is also acceptable, as long as it can be repeated over the duration of the study until confirmed disease progression. 16. Please refer to Table 7 for scheduled BM collection procedures to include aspirate and biopsy. 17. If FISH testing cannot be performed at a local lab the samples can be sent to the central lab. 18. MRD testing by NGS method.
SPEP	X[11]	
Serum immunofixation	X	
Serum FLC assay	X[12]	
IgG, IgM, IgA	X	
IgD or IgE, if applicable	X[13]	
Calcium corrected for albumin (serum)	X	
Skeletal survey	X[14]	
Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET)	X[15]	
BM Aspiration/Biopsy		
BM aspirate and/or core biopsy for local disease assessment	X[16]	
BM aspirate for FISH testing	X[16,17]	
BM aspirate for BCMA expression and biomarker research	X[16]	
BM aspirate for MRD testing	X[16,18]	
If Applicable		
HIV test (if applicable)	X	

Table 4 SoA – Treatment Period for Belantamab Mafodotin Monotherapy CE Phase. Study Assessments to be carried out regardless of whether participant is dosed.

Study Assessments regardless of whether participant is dosed	Day 1 (Week 1)	Treatment Period: Q3W from Week 4 until EOT	Notes
• All assessments will apply to the CE Phase unless otherwise specified. • Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. • Scheduled visit dates during the treatment period can be delayed or brought forward by a maximum of 5 days to be aligned with the next dosing date. If administration of study treatment is delayed ≤7 days, assessments indicated to occur at the dosing visit can be scheduled to occur when dosing occurs (every effort should be made to realign subsequent weekly visits with dosing visits). If administration of study treatment is delayed >7 days, dosing and weekly assessments may occur on the different days.			
AEs/SAEs	Ongoing[1]		1. AEs/SAEs will be collected until at least 70 days after the last dose of study treatment. All SAEs related to study participation (e.g., protocol-mandated procedures, tests or change in existing therapy) are to be collected from consent through OS follow-up. All AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained or the participant is lost to follow-up. For the reporting of ocular events see the guidance provided in Appendix 3.
Concomitant Medications	Ongoing		
Throughout the study, participants are educated about lifestyle considerations (Section 5.3) for the study and the need for maintaining adequate urinary output (Section 2.3.1)	X		2. Informed consent for genetic research must be obtained before collecting a sample. The sample will be collected on C1D1 prior to infusion.
Genetics	X[2]		3. On-study ocular exams to be performed by a qualified eye care specialist (see Appendix 10) every 3 weeks regardless of dosing, up to the sixth dose of belantamab mafodotin (assessment window up to 5 days prior to scheduled visit date, but all effort should be made to schedule as close to belantamab mafodotin dosing as possible). If there are no significant KVA Grade 2 or above treatment-related ocular examination findings, change in participant symptoms or vision at the time of the sixth dose exam, participants may have their ophthalmologic exams decreased to once every 3 months. See Section 8.2.7 for list of ophthalmic exam procedures and frequency of exams.
ECOG Performance Status		X	
Safety			
Ocular Exam		X[3]	
Hematology (CBC)	X[4]	X[4]	4. CBC and chemistry panel may be done more frequently as clinically indicated. Refer to Appendix 2 for comprehensive list of lab tests.
Clinical chemistry	X[4]	X[4]	
eGFR	X[5]	X[5]	5. eGFR as calculated by MDRD formula (Appendix 6).
Urinalysis (dipstick) OR Spot Urine (albumin/creatine ratio)	X[6]	X[6]	6. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥2+, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void).
ECHO or MUGA scan for LVEF		X[7]	7. ECHOs or MUGA scans for LVEF to be done if clinically indicated. The same procedure used at Screening should be used throughout the study.
Disease Evaluation (every 3 weeks even if a dose is delayed)			
UPEP 24 hr urine collection		X[8]	
Urine immunofixation 24 hr urine collection		X[9]	
SPEP		X[8]	
Serum immunofixation		X[9]	

Study Assessments regardless of whether participant is dosed	**Day 1 (Week 1)**	**Treatment Period: Q3W from Week 4 until EOT**	**Notes**
• All assessments will apply to the CE Phase unless otherwise specified. • Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. • Scheduled visit dates during the treatment period can be delayed or brought forward by a maximum of 5 days to be aligned with the next dosing date. If administration of study treatment is delayed ≤7 days, assessments indicated to occur at the dosing visit can be scheduled to occur when dosing occurs (every effort should be made to realign subsequent weekly visits with dosing visits). If administration of study treatment is delayed >7 days, dosing and weekly assessments may occur on the different days.			
Serum FLC assay		X[10]	8. SPEP must be performed Q3W. UPEP will only be performed Q3W for participants who had detectable M-protein only in the urine at screening. For all other participants, if UPEP is negative at screening, then UPEP will be performed only after a tumor response based on SPEP protein during treatment is observed, where UPEP on 24 hours urine sample is required to confirm the response per IMWG criteria.
IgG, IgM, IgA		X	9. To be performed when SPEP or UPEP are negative or not quantifiable. Also to be performed to confirm objective response (PR or better).
IgD or IgE		X[11]	10. Serum Free Light Chain assay will include kappa/lambda ratio and quantification of involved and uninvolved light chains, to be done every 3 weeks.
Calcium corrected for albumin (serum)		X	11. IgD/IgE testing is only required for participants with IgD/IgE myeloma.
Skeletal survey		X[12]	12. Skeletal survey (as clinically indicated): Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). X-ray is acceptable for lytic disease, but other methods are needed (CT, MRI, PET/CT) for assessment of extramedullary disease. Same modality used at Screening should be used throughout study.
Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET)		X[13, 14]	13. Imaging is required for participants with extramedullary disease, as clinically indicated, to document disease response PR or better, or to confirm PD. Imaging is also required when there is a suspected appearance of a new lesion (for confirmation of PD). To be performed by the same method throughout the study as was done at baseline (ie, if CT/PET scan was used as baseline, participant needs to be followed by CT/PET scans). Selected target lesions need to be measured.
MRI, CT or PET/CT upon achieving CR or sCR		Once after CR or sCR[14]	14. **Note**: Germany: no PET/CT will be performed until approval by the German Federal Office for Radiation Protection.
BM Aspiration/Biopsy			15. Please refer to Table 7 for scheduled BM collection procedures to include aspirate and biopsy.
BM aspirate for BCMA expression and biomarker research		X[15]	16. Assessed in CE Phase only.
BM aspirate for MRD testing		X[15]	17. OSDI will be performed at Day 1 (Week 1), at / or directly after C4D1 and at EOT only. Additional assessments may be conducted for those participants who are experiencing a worsening in visual function.
BM aspirate and/or core biopsy for local Disease assessment		X[15]	18. Collected predose at Day 1 (Week 1) and then every 6 weeks until EOT.
BM core biopsy to assess sCR (local)		X[15]	
Health Outcomes (CE only)[16]			
PRO-CTCAE	X	X	
OSDI	X[17]	X[17]	
EORTC QLQ-C30 and EORTC IL52	X[18]	X[18]	

Table 5 SoA – Treatment Period on Dosing Days or After Dosing Only: Regarding Belantamab Mafodotin Monotherapy CE Phase

Study Assessments	Cycle 1 Day 1 (Week 1)	Cycle 1 Day 8 Day 15	Cycle 2 to EOT	Notes
• All assessments will apply to the CE Phase unless otherwise specified. • Assessments should be done prior to drug administration, unless otherwise specified. • From Cycle 2, assessments can be performed ≤3 days prior to the scheduled date unless otherwise specified. • **If C1D1 Hem/Chem results are outside of the eligibility requirements, Medical Director to be contacted for review prior to dosing**.				
Safety				1. Measured after resting for at least 5 min. For first infusion, vital signs must be monitored at predose (within 30 min prior to SOI, and at the EOI [+0-10 min], and 1 h post EOI [+0-10 min]). For subsequent infusions, vital signs must be monitored at predose (within 30 min prior to each SOI, and at each EOI (+0-10 min), and 30 min post each EOI (+0-10 min) and as clinically indicated. On dosing days with PK sampling time points, if vital signs are conducted, they should be assessed prior to PK samples being drawn. The timing of the assessments should allow the blood draw to occur at the exact nominal time. 2. On-study ocular exams to be performed by a qualified eye care specialist (see Appendix 10) regardless of dosing up to the sixth dose of belantamab mafodotin (assessment window up to 5 days prior to dosing, but all effort should be made to schedule as close to belantamab mafodotin dosing as possible). If there are no significant KVA Grade 2 or above treatment-related ocular examination findings, change in participant symptoms or vision at the time of the sixth dose exam, participants may have their ophthalmologic exams decreased to once every 3 months. See Section 8.2.7 for list of ophthalmic exam procedures and frequency of exams. 3. Perform only in women of childbearing potential. Pregnancy tests may be either predose serum or urine and should be performed within 72 hours prior to each dose of belantamab mafodotin. 4. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥2+, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void). 5. If already completed within 72 hours prior to dosing, this assessment does not need to be repeated on Day 1 of the cycle. Refer to Appendix 2 for comprehensive list of lab tests. CBC and chemistry panel may be done more frequently as clinically indicated. 6. eGFR as calculated by MDRD formula (Appendix 6).
Physical Exam (full exam on treatment days Day 1 of each cycle, and C1D8 only)	X	X	X	
Vital Signs (BP, HR, Body Temperature)	X[1]	X[1]	X[1]	
Ocular Exams	X[2]		X[2]	
Weight	X		X	
Pregnancy Test	X[3]		X[3]	
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[4]		X[4]	
Hematology (CBC)	X[5]	X[5]	X[5]	
Clinical chemistry	X[5]	X[5]	X[5]	
eGFR	X[6]	X[6]	X[6]	

ECOG Performance Status	X		X
PK and ADA			
Plasma PK for belantamab mafodotin	X[7]	X[7]	X[7]
Serum immunogenicity (ADA) for belantamab mafodotin	X[8]		X[8]
Biomarkers			
Serum soluble BCMA	X[9]	X[9]	X[9]
Hematology (TBNK and/or enhanced TBNK cell activation panel)	X[10]		X[10]
Peripheral blood for CMMC analysis	X[11]		X[11]
Treatment with belantamab mafodotin			
Administration of belantamab mafodotin	X[12]		Day 1 of each Cycle[12]
Premedication if needed	X[13]		X (at the start of each cycle)[13]
Treatment prophylaxis and management: Preservative-free artificial tears and cooling masks	X[14]		X[14]

7. PK samples to be taken for all participants for belantamab mafodotin: C1D1 – predose (within 30 minutes prior to belantamab mafodotin SOI), EOI (0 – 10 min after belantamab mafodotin); at 2 h (±15 min) after belantamab mafodotin SOI; C1D8 – anytime; not required on C1D15. C2D1 – predose (within 30 min prior to belantamab mafodotin SOI) (if belantamab mafodotin dosing at C2D1 is delayed, belantamab mafodotin PK sample still to be collected per laboratory manual); C2D1 EOI (0 – 10 min after belantamab mafodotin EOI); C4D1, C6D1, C9D1, and C12D1– predose (within 30 min prior to belantamab mafodotin SOI) and EOI (0 – 10 min after belantamab mafodotin EOI), and C18D1 – predose (within 30 min prior to belantamab mafodotin SOI) or up to the primary cutoff date or closure of sub-study by sponsor, whichever comes first.
8. ADA serum samples will be collected predose (within 30 minutes prior to belantamab mafodotin SOI) at: Cycles 1, 2, 4, 6, 9, 12 and 18 or up to the primary cutoff date or closure of sub-study by sponsor, whichever comes first.
9. Collect a sBCMA serum sample every time a belantamab mafodotin PK sample is collected. Also collect sBCMA at every MRD assessment and at EOT.
10. To be collected prior to dosing at C1D1, C2D1, C3D1, and at PD.
11. Collect prior to belantamab mafodotin infusion at C1D1, C2D1, C3D1, C4D1 and C6D1. Also, at first MRD assessment and at EOT.
12. Please refer to Section 6.6.3 and Section 6.6.4 of the protocol for guidance on dose delays, reduction and modification. The next scheduled dose must be administered every 21 days (+3-day window) since prior/last dose and cannot be given sooner/more frequently than this. If in the judgment of the investigator, treatment needs to be initiated prior to the next planned scheduled dose *following a dosing delay and where clinical toxicity has resolved*, please discuss with the Medical Director. Please see Section 6.2. All assessments should remain on schedule with the exception of those associated with dosing. Belantamab mafodotin will be administered as an IV infusion (see Section 6.1 for details).
13. Premedication should be considered in any participant who experienced an infusion-related reaction at first or any subsequent infusion with belantamab mafodotin or partner combination see relevant sub-study protocol section.
14. Supportive Care information:
    a. Prophylactic preservative-free artificial tears should be administered in each eye at least 4-8 times daily beginning on C1D1 until end of treatment. In the event of ocular symptoms (e.g., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed. Corticosteroid eye drops are not required but can be used if clinically indicated per the discretion of a qualified eye care specialist (see Appendix 10). Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered).
    b. At the start of each infusion, participants may apply cooling eye masks to their eyes for approximately 1 hour or as long as tolerated.

				c. For participants with history of dry eyes, or participants who develop dry eye during study treatment, the eye care specialist should consider use of additional products/treatments as per local institutional guidance.

Table 6 SoA –EOT and Follow-up: Regarding Belantamab Mafodotin Monotherapy for all Sub-studies

Study Assessments	End of Treatment Visit[1]	PFS Follow-up[2]	OS Follow-up[3]	Notes
All assessments will apply to both the DE and CE Phases unless otherwise specified.				
Physical Exam	X	X		1. EOT safety assessments to occur within 30 days from decision to discontinue treatment and at least prior to the new anti-MM treatment. 2. PFS follow-up every 21 days (±7 days) for participants who discontinue IP for a reason other than PD. Disease evaluations will continue until confirmed PD, death, start of a new anti-cancer treatment, withdrawal of consent, or end of the study whichever occurs first. Once participant progresses, move to OS Follow-up. 3. The survival for MM will be documented in medical charts. No visit necessary. Contacts will be made via phone calls, emails or other means of communication every 12 weeks (±14 days) until end of study. Participant does not need to come in for visit unless they are being followed for corneal signs that are present at the end of study treatment. 4. AEs/SAEs will be collected from the start of study treatment until at least 70 days after the last dose of study treatment. All SAEs related to study participation (e.g., protocol-mandated procedures, tests or change in existing therapy) are to be collected from consent through OS follow-up. All AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained or the participant is lost to follow-up. Concomitant medications administered after EOT should be recorded when given for SAEs/AESIs as defined in Section 8.3. 5. End of treatment ophthalmic exam to be performed by an eye care specialist. See Section 8.2.7 for list of exams. 6. Participants with treatment-related corneal exam findings, ocular symptoms and/or change in vision at EOT will be followed every 3 months (±7 days), or more frequently if clinically indicated, until return to baseline, deemed clinically stable by the qualified eye care specialist (see Appendix 10), or up to 12 months (whichever comes first). Clinically stable is defined as changes ≤Grade 1. See Section 8.2.7 for list of exams.
Vital Signs (BP, HR, Body Temperature)	X	X		
AEs/SAEs	X[4]	Related SAEs only[4]	Related SAEs only[4]	
Concomitant Medications	X[4]	X[4]		
Safety				
Ocular Exam	X[5,6]	X[6]	X[6]	
ECOG Performance Status	X	X		
Hematology (CBC)	X[7]	X[7]		
Clinical chemistry	X[7]	X[7]		
Pregnancy Test	X[8]	X[8]	X[8]	
eGFR	X[9]			
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[10]			
ECHO or MUGA scan for LVEF	X[11]			
Disease Evaluation				
UPEP 24 hr urine collection	X[21]	X[21]		
Urine immunofixation 24 hr urine collection	X	X		
SPEP	X	X		
Serum immunofixation	X	X		
Serum FLC assay	X	X		
IgG, IgM, IgA	X	X		
IgD or IgE	X[12]	X[12]		
Calcium corrected for albumin (serum)	X	X		
Skeletal survey	X[13,14]	X[13,14]		

Study Assessments	End of Treatment Visit[1]	PFS Follow-up[2]	OS Follow-up[3]	Notes
All assessments will apply to both the DE and CE Phases unless otherwise specified.				
Imaging for Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET)	X[14,15]	X[14,15]		7. CBC may be done more frequently as clinically indicated. Refer to Appendix 2 for a comprehensive list of lab tests that must be collected for all participants. 8. Pregnancy test (serum or urine) must be performed per Appendix 7, Section 12.7.3. See specific sub-studies for any additional criteria. 9. eGFR as calculated by MDRD formula (Appendix 6). 10. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥2+, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void). 11. ECHO or MUGA scan for LVEF only done as clinically indicated. The same procedure used at Screening should be used throughout the study. 12. IgD/IgE testing is only required for participants with IgD/IgE myeloma. 13. Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). X-ray is acceptable for lytic disease, but other methods are needed (CT, MRI, PET/CT) for assessment of extramedullary disease. Skeletal survey results within 30 days prior to C1D1 may be used for Screening. Same modality used at Screening should be used throughout study. 14. At the time of suspected disease progression or as clinically indicated. Same modality used at Screening should be used throughout study. 15. In participants with extramedullary MM, if the last radiographic assessment occurred ≥8 weeks prior withdrawal from study treatment, and PD has NOT been documented otherwise, a new assessment should be obtained at the time the participant withdrew from study treatment. To be performed by the same method throughout the study as was done at baseline (ie, if CT/PET scan was used as baseline, participant needs to be followed by CT/PET scan). 16. Please refer to Table 7 for scheduled BM collection procedures to include aspirate and biopsy.
PK and ADA				
Plasma PK for belantamab mafodotin	X			
Serum immunogenicity (ADA) for belantamab mafodotin	X			
Biomarkers				
Serum soluble BCMA	X			
Peripheral blood for CMMC analysis	X			
BM Aspiration/Biopsy				
BM aspirate for MRD testing		X[16]		
BM aspirate and/or core biopsy for local Disease assessment	X[16]	X[16]		
BM core biopsy to assess sCR (local)	X[16]	X[16]		
BM aspirate for BCMA expression and biomarker research	X[16]			
Health Outcomes				
PRO-CTCAE	X[17]			
OSDI	X[17,18]	X[17,18]	X[17,18]	
EORTC QLQ-C30 and EORTC IL52	X[17]			
Qualitative interview	X[17,19]	X[17,20]	X[17,20]	

Study Assessments	End of Treatment Visit[1]	PFS Follow-up[2]	OS Follow-up[3]	Notes
All assessments will apply to both the DE and CE Phases unless otherwise specified.				
Schedule Survival Status phone call	X[3]		X[3]	17. Questionnaires and Interviews only performed in CE. 18. Participants with treatment-related corneal exam findings, ocular symptoms and/or change in vision at EOT will have follow-up OSDI questionnaires every 3 months (±7 days) until return to baseline, deemed as clinically stable by the qualified eye care specialist (see Appendix 10), or up to 12 months (whichever comes first). Clinically stable is defined as changes ≤Grade 1. 19. Must be conducted via telephone within approximately 21 days of EOT. 20. Optional interview to be conducted via telephone approximately 6 months after EOT. 21. UPEP will only be performed for participants who had detectable M-protein only in the urine at screening. For all other participants, if UPEP is negative at screening, then UPEP will be performed only after a tumor response based on SPEP protein during treatment is observed, where UPEP on 24 hours urine sample is required to confirm the response per IMWG criteria.

Table 7 SoA – Bone Marrow Aspirate/Biopsy Collection

Timepoint	BM aspirate for FISH testing[1,3]	BM (core biopsy and/or aspirate) for disease assessment[1]	BM aspirate for MRD testing for disease assessment[2,6]	BM aspirate for BCMA expression and biomarker research[2]
Screening	X[4]	X[4]	X	X
Between C3D1 and C5D1 (predose belantamab mafodotin)				X[7]
VGPR or suspected CR/sCR	X[5]	X[5]	X	
Suspected PD (only if PD not evident otherwise)		X[5]		
PD				X[7]

1. These assessments will be performed at a local laboratory. For FISH testing, if testing cannot be performed at a local lab the samples can be sent to the central lab.
2. These assessments will be performed at a central laboratory.
3. See Table 31 for details on FISH.
4. At Screening, IHC of BM core biopsy is preferred for quantitative assessment of malignant PC. However, BM aspirate is acceptable and should be performed within 60 days of C1D1. Archival tissue from up to 60 days prior to C1D1 is acceptable.
5. At EOT or during PFS follow-up Visit, only to confirm CR/sCR or suspected PD at this visit for plasma cell assessment by IHC or aspiration. For sCR in participants achieving a CR, BM core biopsy is required to confirm sCR by IHC for absence of clonal cells. Only 1 marrow procedure required for CR and sCR assessment.
6. MRD samples to be collected at Screening, and at the time of first achieving VGPR or better. Thereafter, MRD testing must be repeated every 6 months (±1 month) until PD. This also applies to participants who discontinue IP for reasons other than PD and have current disease response of VGPR or better. In case of deepening of response from VGPR to CR, or achieving CR without prior VGPR, MRD testing must be performed at the time of achieving suspected CR and repeated every 6 months (±1 month) until PD.
7. **Optional BM consent required.** Additional BM aspirate samples may be collected at any time during the study for biomarker research (as indicated for each sub-study) and if possible, as part of the same BM collection for disease assessments including MRD.

Table 8 SoA – Additional Procedures for Participants HbcAb Positive

The procedures listed in this table apply ONLY to participants in Screening or who have been enrolled and who have positive HbcAb; all procedures must be done in addition to the required procedures for all participants detailed in Table 3, Table 4, Table 5, Table 6, Table 7.

HBV Study Assessments	During Screening / Prior to starting treatment	During Treatment	EOT	Notes
HBV-DNA testing	X	X	X	HBV-DNA testing prior to the start of belantamab mafodotin and subsequently every 3 months (may be grouped with closest study visit), or if liver function test elevations requiring increased monitoring or stopping criteria occur, or for any clinical suspicion of hepatitis reactivation.

2. INTRODUCTION

2.1. Study Rationale

MM is an incurable malignancy and accounts for 1% of all cancers and for 10% of all hematologic malignancies. Worldwide, approximately 139 000 new cases are diagnosed annually [Cowan, 2018], and an estimated 30 770 new cases and 12 770 deaths will occur in the U.S. in 2018 [Siegal, 2018]. Despite significant advances, current novel therapies and HSCT cannot achieve cure, and most MM participants will die of disease progression or complications of myeloma. Thus, new treatments are urgently needed.

BCMA is a target present on mature B-cells and on tumor cells in patients with MM [Tai, 2015; Tai, 2006]. Belantamab mafodotin is an ADC consisting of a humanized anti-BCMA mAb that is conjugated to the microtubule inhibitor MMAF with a cysteine linker (cys-mcMMAF; also, known as [redacted]. Upon binding to the cell surface, belantamab mafodotin is rapidly internalized and active cytotoxic drug (cys-mcMMAF) is released inside the cell. Additionally, the antibody is afucosylated, which increases binding to FcγRIIIa receptors and enhances recruitment and activation of immune effector cells, which can kill tumor cells by ADCC. Belantamab mafodotin employs distinct MoAs including ADC, ADCC and ADCP. The mechanisms of action of belantamab mafodotin are designed to enable anti-tumor activity of cells by ADCC (nondividing) as well as ADC (dividing cells). Moreover, ADC-induced cell death by belantamab mafodotin was recently shown to be immunogenic as measured by cell surface externalization of CRT and secretion of HMGB1 and ATP. ICD induced by belantamab mafodotin resulted in activation of dendritic cells in vitro and is believed to contribute to T cell-mediated anti-tumor responses and durable immunity.

Of the 4 proposed MoA for belantamab mafodotin, the ADC and ADCC MoAs have been linked to efficacy in nonclinical models: in vitro and in vivo against multiple myeloma cell lines, and ex vivo against primary patient myeloma samples. Inhibition of BCMA signaling has been demonstrated biochemically; however, functional effects on myeloma cells have not been demonstrated. ICD markers on cells are induced by belantamab mafodotin both in vivo and in vitro. In vivo, induction of ICD correlates with an adaptive immune response and long-term tumor regression in immune-competent murine allograft models [Montes De Oca, 2021]. These different mechanisms may enable belantamab mafodotin to deliver anti-tumor activities targeting both dividing and nondividing tumor cells and associate the cell kill with an adaptive immune response. These MoA characteristics clearly differentiate belantamab mafodotin from existing approved treatments. Several assets targeting BCMA by different mechanisms are in clinical development for MM, including BCMA CAR-T cells and BCMA bispecific antibodies. However, none of the currently approved therapies for MM have the same MoAs as belantamab mafodotin.

Despite new medicines in a relapsed refractory population providing clinical benefit, multiple myeloma is not currently curable and an unmet need still remains. Belantamab mafodotin has shown strong single-agent activity in the FTIH (BMA117159/DREAMM-1 and the Phase 2 205678/DREAMM-2 studies) (see Section 2.2.4).

Due to the novel MoA of belantamab mafodotin, it is possible that belantamab mafodotin may be able to overcome resistance to existing therapies.

The efficacy for belantamab mafodotin monotherapy is reviewed in the IB (see also Section 2.2.4) [GlaxoSmithKline Document Number GSK2857916. Investigator's Brochure V11, 2023].

Given this previous experience, the combination therapy of belantamab mafodotin with other agents with different MoA is an attractive option to explore for participants with MM who have relapsed or become refractory to SoC. The combination with other agents may result in additive, or potentially synergistic effects which could translate into deep and long-lasting responses. This study will first evaluate the safety and tolerability profile of belantamab mafodotin when administered in combination with other agents and may identify one or more RP2Ds for each partner, as well as preliminary efficacy of each combination (DE Phase). The CE Phase of the study will evaluate the clinical activity of the combinations in comparison to monotherapy in additional participants with RRMM. The combination agents for each sub-study of this platform design will be chosen based on scientific rationale and/or available preclinical data.

The platform design is an efficient tool, incorporating a single MP, wherein, multiple treatment combinations, as sub-studies, will be evaluated simultaneously. Randomization between arms and against the monotherapy control arm will lead to a generation of robust statistical data in the CE Phase to inform future confirmatory studies. The platform design allows for the introduction of new sub-studies with potentially different control groups as treatment paradigms evolve. Detailed information for each individual combination is provided in the respective sub-study protocol section.

2.2. Background

2.2.1. Current Treatment of Multiple Myeloma

Most, if not all participants treated with myeloma regimens inevitably relapse, with a median OS of about 5 years [Robinson, 2014; Hou, 2017; Palumbo, 2015]. Each relapse requires salvage therapy, and the DoR to each subsequent line of salvage therapy typically decreases. For example, in a retrospective chart review by Kumar et al. [Kumar, 2012] of patients who become refractory to bortezomib and immunomodulatory agents, the median overall survival time was disappointingly short (~ 9 months), with 7% achieving VGPR, 24% achieving PR, and 10% with stable disease after retreatment. While the main treatment goal for RRMM is usually the preservation of organ function, control of the disease, and maintaining quality of life, the depth of response is also considered a predictor of durability of response and patient survival [Lonial, 2014].

While combining agents with existing SoC therapies might be a straightforward approach, an alternative strategy to achieving deep responses is to evaluate combinations of agents that have preclinical evidence or scientific rationale for enhancing the clinical benefit of belantamab mafodotin.

2.2.2. Role of B-Cell Maturation Antigen in Multiple Myeloma.

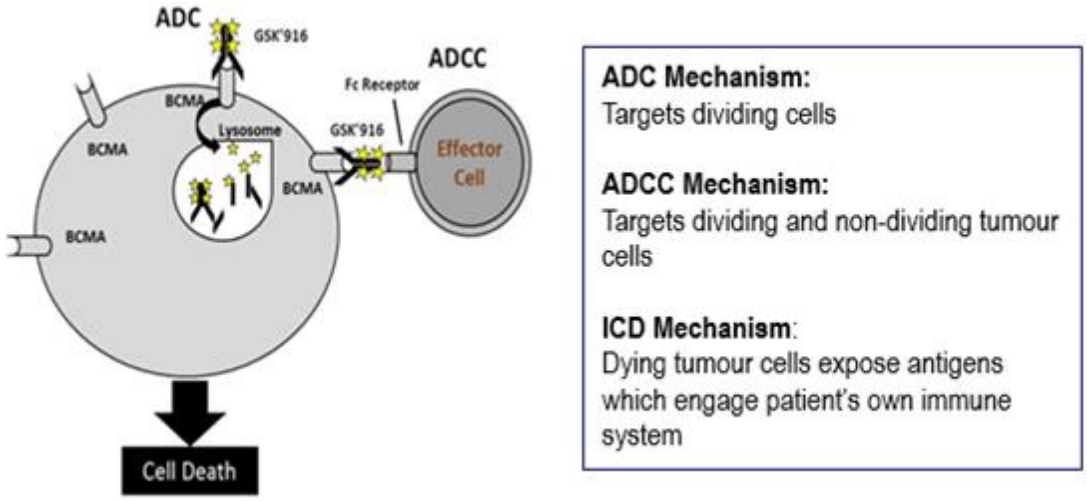
BCMA, also designated as tumor necrosis factor receptor superfamily member 17 (TNFRSF17) is expressed on the surface of normal and malignant B lymphocytes at later stages of differentiation as they mature [Novak, 2004]. Ligands targeting BCMA such as BAFF, TNFSF13B, along with APRIL/TNFSF13 activate cell proliferation pathways and upregulate anti-apoptotic proteins in MM cell lines [Bellucci, 2005; Moreaux, 2004]. sBCMA is present in the serum of MM patients, and its levels have been postulated to correlate with tumor burden, response to therapy and OS [Robinson, 2014; Sanchez, 2012]. Mice deficient for BCMA are viable, have normal B-cell development, and exhibit normal humoral responses [Belnoue, 2008; Jiang, 2011; Varfolomeev, 2004]. BCMA is widely expressed on malignant plasma cells in MM and to a lesser degree in other B-cell malignancies [Tai, 2015; Tai, 2006]. The restricted expression profile of BCMA makes it a very good target for a therapeutic antibody with direct cell killing activity and expected to have limited off target effects [Tai, 2015].

BCMA has been validated as a therapeutic target in MM in preclinical studies [Tai, 2014] and more recently in the clinic, where impressive results were demonstrated with BCMA-targeted CAR-T [Pont, 2019], and belantamab mafodotin as single agent [GlaxoSmithKline Document Number GSK2857916. Investigator's Brochure V11, 2023; Trudel, 2018; Trudel, 2019].

2.2.3. Antibody-Drug Conjugate Belantamab Mafodotin

Belantamab mafodotin is a humanized (IgG1) ADC which binds specifically to BCMA with different mechanisms of action as detailed in the investigator brochure. Of the 4 proposed MoA for belantamab mafodotin, the ADC and ADCC MoAs have been linked to efficacy in nonclinical models: in vitro and in vivo against multiple myeloma cell lines, and ex vivo against primary patient myeloma samples. These different mechanisms may enable belantamab mafodotin to deliver anti-tumor activities targeting both dividing and nondividing tumor cells and associate the cell kill with an adaptive immune response; these MoA characteristics clearly differentiate belantamab mafodotin from existing approved treatments. All patients with MM express various levels of BCMA on the surface of the tumor cells, making them potentially responsive to treatment with belantamab mafodotin [Darce, 2007].

Figure 2 Mechanism of action of belantamab mafodotin



2.2.4. Human Experience with Belantamab Mafodotin

GSK initiated the clinical development of belantamab mafodotin in July 2014, with the FTIH Study BMA117159 (DREAMM-1) conducted in adults with RRMM. DREAMM-1 has been clinically concluded. The primary analysis of data from participants with MM obtained during Part 1 and Part 2 of the study has been reported; however, the study is considered ongoing.

The pivotal Phase 2 Study 205678 (DREAMM-2) is ongoing and evaluating the efficacy and safety of 2 doses of belantamab mafodotin monotherapy in RRMM refractory to proteasome inhibitors, immunomodulatory drugs and who failed anti-CD38 antibody treatment. The primary analysis has been reported; however, the study is considered ongoing.

Single-agent belantamab mafodotin has demonstrated to have a strong single-agent activity with a well-defined manageable safety profile in heavily pre-treated participants with RRMM (Q3W schedule via IV administration). Safety data for single-agent belantamab mafodotin were pooled (data as of 20 September 2019) for Study 205678 (DREAMM-2; NCT03525678) and supportive FTIH study BMA117159 (DREAMM-1; NCT02064387), by treatment cohorts of 2.5 mg/kg and 3.4 mg/kg.

FTIH study BMA117159/DREAMM-1

In the FTIH DREAMM-1 study, which consisted of a dose escalation phase (Part 1, n=38) and a dose expansion phase (Part 2, n=35), as of the primary analysis cutoff date of 31 August 2018, a total of 73 participants with RRMM received at least 1 dose of belantamab mafodotin [GlaxoSmithKline Document Number GSK2857916. Investigator's Brochure V11, 2023; Trudel, 2019].

As of the efficacy cutoff date of 31 August 2018, a total of 35 participants were treated at the 3.4 mg/kg dose in Part 2 of the DREAMM-1 study. Participants were heavily

pre-treated: 57% of participants had 5 or more prior lines of therapy. The ORR was 60% (95% CI: 42.1, 76.1): comprised of PR, 6%; VGPR, 40%; CR, 9%; and sCR, 6%. The median DoR was 14.3 months (95% CI: 10.6, NR). The mPFS in this population was 12.0 months (95% CI: 3.1, not estimable [NE]). For participants refractory to both immunomodulatory agents and PIs (n=32/35), the confirmed ORR was 56% (95% CI: 37.7, 73.6) and mPFS was 7.9 months (95% CI: 2.3, NE) [Trudel, 2019].

Phase 2 Study 205678/DREAMM-2

The ongoing Phase 2 Study 205678/DREAMM-2 is evaluating these 2 IV single-agent doses (2.5 and 3.4 mg/kg) administered Q3W until disease progression in participants who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an immunomodulatory agent and a proteasome inhibitor. A total of 194 participants received frozen drug product in the main cohort and 24 participants received 3.4 mg/kg lyophilized drug product. The study met its primary endpoint for ORR in both the 2.5 mg/kg and 3.4 mg/kg treatments, and the benefit of belantamab mafodotin was supported by the secondary endpoints. Primary analysis data from this study indicated no new safety signals, and the profile of AEs was similar to the experience in the DREAMM-1 study for both arms. Both dose levels, 2.5 and 3.4 mg/kg, were shown to have a positive benefit/risk profile [Li, 2017; Lonial, 2020].

As of the cutoff date of 31 January 2020, the ORR in the 2.5 mg/kg treatment was 31% (97.5% CI 21.7,43.6) and in the 3.4 mg/kg treatment 35% (97.5% CI 24.8,47.0). The median DoR was 11.0 months (95% CI: 4.2, NR) at 2.5 mg/kg and 6.2 months (95% CI: 4.8, NR) at 3.4 mg/kg. The mPFS in this population was 2.8 months (95% CI: 1.6, 3.6) and 3.9 months (95% CI: 2.0, 5.8), respectively and the median Overall Survival (mOS) was 13.7 months (95% CI: 9.9, NR) at 2.5 mg/kg and 13.8 months (95% CI: 10.0, NR) at 3.4 mg/kg. Positive clinical activity was also demonstrated at the 3.4 mg/kg lyophilized dose [ORR 52% (97.5% CI 28.9,74.5)].

Safety

Single-agent belantamab mafodotin was demonstrated to have a manageable safety profile in heavily pre-treated participants with RRMM. Safety data for single-agent belantamab mafodotin were pooled (data as of 20 September 2019) for DREAMM-2 study and supportive FTIH study DREAMM-1 by treatment cohorts of 2.5 mg/kg and 3.4 mg/kg.

The most common AEs in both treatment cohorts were keratopathy (corneal epithelium changes observed on ophthalmic examination), thrombocytopenia and anemia. The incidence of AEs, including Grade 3/4 AEs was comparable between belantamab mafodotin 2.5 mg/kg and 3.4 mg/kg cohorts. AEs leading to dose delays, and reductions were less frequent in 2.5 mg/kg cohort, 51% and 32% compared with the 3.4 mg/kg cohort, 67% and 52%, respectively. AEs leading to permanent treatment discontinuation occurred in 10% and 11% of participants in the 2.5 and 3.4 mg/kg cohorts, respectively. More participants in the 3.4 mg/kg cohort experienced SAEs (50%) and fatal SAEs (6%) compared with the 2.5 mg/kg cohort (41% and 3%, respectively).

Single-agent belantamab mafodotin 2.5 mg/kg was selected as the recommended dose based on comparable efficacy with a more favorable safety profile (ie, lower incidence of thrombocytopenia and neutropenia and less frequent dose delays or reductions) compared with the 3.4 mg/kg dose.

Adverse Events of Special Interest

AESIs for belantamab mafodotin are corneal events, thrombocytopenia and IRRs, and are described below.

Corneal Events

Corneal events, reported in most cases as keratopathy, blurred vision and dry eye events are the most frequently reported AEs with belantamab mafodotin.

In DREAMM-2 (data as of 31 January 2020), events in the Eye disorders SOC occurred in 78% of participants treated with belantamab mafodotin 2.5 mg/kg. The most common ocular AEs were keratopathy (71%, changes in corneal epithelium identified on eye exam, with or without symptoms), blurred vision (22%), and dry eye (13%). Decreased vision defined as Snellen score worse than 20/50 in the better seeing eye was reported in 18% of participants receiving belantamab mafodotin 2.5mg/kg. Severe vision loss defined as 20/200 or worse in the better seeing eye was reported in 1% of participants receiving belantamab mafodotin 2.5 mg/kg.

The median time to onset of Grade 2 or above corneal findings (best corrected visual acuity or corneal examination) was 36 days (range: 19 to 143 days) in participants receiving belantamab mafodotin 2.5 mg/kg. The median time to resolution of these corneal findings was 91 days (range: 21 to 201 days).

Participants with history of dry eye were more prone to develop corneal examination findings. Therefore, active management of dry eye symptoms prior to and during treatment is recommended (ie, administration of preservative-free artificial tears).

The ocular sub-study of DREAMM-2 provided no evidence that corticosteroid eye drops are beneficial in preventing or mitigating corneal events.

Thrombocytopenia

In DREAMM-2 (data as of 31 January 2020), thrombocytopenic events (thrombocytopenia and platelet count decreased) occurred in 38% participants treated with belantamab mafodotin 2.5 mg/kg; severity ranging between Grade 1 and 4. The incidence of Grade 3 bleeding events was low (2%), with no Grade 4 or 5 events reported in participants treated with belantamab mafodotin 2.5 mg/kg.

Most participants had a decrease from baseline in their platelet counts during the study. In general, participants who initiated treatment with lower platelet numbers tended to continue to have thrombocytopenia while on treatment with belantamab mafodotin.

Infusion-related reactions

IRRs are expected for biologic agents. In DREAMM-2 (data as of 31 January 2020), IRRs occurred in 21% of participants in the belantamab mafodotin 2.5 mg/kg, which were Grade 1 – 3 in severity. Most IRRs occurred with the first infusion and few participants experienced IRRs with subsequent infusions.

Although not protocol-mandated, premedications for IRR prophylaxis (including paracetamol, antihistamines, and steroids) were administered to 26%–27% of participants. One participant (2.5 mg/kg cohort) discontinued treatment due to IRRs (Grade 3 IRRs at first and second infusion).

2.2.4.1. Pharmacokinetics and Pharmacodynamics in Humans

The PK and pharmacodynamics of belantamab mafodotin (antibody-drug conjugate, including in complex) and total monoclonal antibody (total mAb; including complex) were investigated in 291 participants with RRMM following IV administration at doses from 0.03 to 4.6 mg/kg Q3W in Study BMA117159 (n=73) and at doses of 2.5 or 3.4 mg/kg Q3W in Study 205678 (n=218).

Cmax of belantamab mafodotin and total monoclonal antibody were observed at or shortly after the EOI. There was limited accumulation (less than 2-fold) of belantamab mafodotin during subsequent cycles.

Belantamab mafodotin PK were well described by a linear, two-compartment population model, with a time-varying decrease in clearance in a population PK analysis. Belantamab mafodotin had a systemic clearance of 0.936 L/day and an elimination half-life of 11.5 days for a typical participant with relapsed/refractory multiple myeloma at Cycle 1 in Study 205678. Over time, clearance was reduced by an average of 28% to 0.674 L/day with an elimination half-life of 14.3 days (time-varying clearance). In summaries of individual post hoc parameter values from the population PK model, the geometric mean (%CVb) clearance at first cycle was 0.924 L/day (42%), and the geometric mean (%CVb) half-life value was 11.8 days (37%) at the first cycle. The time to 50% change in clearance was approximately 50 days.

No clinically significant differences in the PK of belantamab mafodotin were observed based on age (34 to 89 years), sex, race (African American/Black and White), body weight (42 to 130 kg), mild or moderate renal impairment (eGFR $\geq$30 mL/min/1.73m^2) or mild hepatic impairment (NCI-ODWG classification). Higher serum levels of Beta-2 microglobulin, IgG, and sBCMA and lower levels of albumin are associated with more advanced multiple myeloma or a higher multiple myeloma disease burden. Higher baseline IgG and sBCMA levels, and lower baseline albumin levels were associated with higher belantamab mafodotin clearance leading to lower average and trough concentrations of belantamab mafodotin.

In nonclinical studies, cys-mcMMAF had limited metabolic clearance. In vitro data suggested that belantamab mafodotin and cys-mcMMAF are unlikely to perpetrate a drug-drug interaction or to be a victim of a drug-drug interaction with inhibitors or inducers of cytochromes (CYP) P450. Cys-mcMMAF was an in vitro substrate of organic

anion transporting polypeptides (OATP)1B1 and OATP1B3, multidrug resistance associated proteins (MRP)1, MRP2, and MRP3, a borderline substrate of bile salt export pump (BSEP), and a possible substrate of P-glycoprotein (Pgp). Following the administration of belantamab mafodotin to participants with RRMM, only intact cys-mcMMAF was detected in pooled CCI [redacted] with no evidence of other MMAF-related CCI [redacted] metabolites.

Free sBCMA levels were measured in Study BMA117159 and Study 205678. All participants exhibited reductions in free sBCMA concentration at end of infusion compared to baseline at Cycle 1, with a return to near-baseline level by 7 days after dosing, reflecting binding of belantamab mafodotin to sBCMA. Maximum decreases ranged from 2% to 97%, which were qualitatively dose-dependent, with larger reductions in free sBCMA at higher doses.

Exposure-response analyses performed for Study 205678 and/or Study BMA117159 found that ocular safety endpoints were most strongly associated with belantamab mafodotin exposure, while efficacy endpoints had a weaker association with belantamab mafodotin exposure. Both safety and efficacy endpoints were associated with patient characteristics. Belantamab mafodotin trough concentrations were associated with probability of corneal events and keratopathy. Probability of occurrence of dry eye, blurred vision, neutropenia and IRR were not associated with an exposure measure. In addition, the results of the concentration-QTc analysis demonstrated that belantamab mafodotin did not have a significant effect on cardiac repolarization.

Additional updated information related to belantamab clinical PK, pharmacodynamics, and exposure-response relationships can be found in the Investigator's Brochure [GlaxoSmithKline Document Number GSK2857916. Investigator's Brochure V11, 2023].

2.2.4.2. Combination with Belantamab Mafodotin

Rationale for each individual experimental treatment is provided in the respective sub-study protocol section.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of belantamab mafodotin may be found in the IB [GlaxoSmithKline Document Number GSK2857916. Investigator's Brochure V11, 2023].

Benefits and risks for each combination partner can be found in the respective sub-study protocol section.

2.3.1. Summary of Risk Assessment

Table 9 Risk Assessment for Belantamab Mafodotin

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product: Belantamab Mafodotin		
Keratopathy (changes to the corneal epithelium, potentially resulting in vision changes)	Changes in corneal epithelium on ocular examination have been frequently observed with belantamab mafodotin and was most commonly associated with keratopathy (changes in the corneal epithelium upon examination), blurred vision, dry eyes, photophobia and changes in visual acuity. Participants with a history of dry eye were more prone to develop changes in the corneal epithelium. Based on available follow-up data, vision returned to, or near, baseline in most cases.	• Active monitoring for changes in corneal epithelium according to SoA tables (Section 1.3). • Evaluation and management by an eye care professional. • Dose modification guidelines are outlined in Section 6.6.
Thrombocytopenia	Belantamab mafodotin may cause transient thrombocytopenia in some participants, which for most cases, recovered between doses. In the pooled safety population of Study 205678, which included participants treated with belantamab mafodotin 2.5 and 3.4 mg/kg, thrombocytopenia was noted in 46% of participants and ranged between Grade 1 to 4 in severity.	• Routine monitoring of hematologic panels as outlined in the SoA (Section 1.3). • Supportive therapy per local medical practice (e.g., platelet transfusion). • Dose modification guidelines are outlined in Section 6.6.
Nephrotoxicity	Nonclinical safety experiments have demonstrated primary glomerular injury and tubular degeneration/regeneration (in rat and monkey). These morphologic changes were accompanied by large molecular weight proteinuria (albuminuria) and enzymuria. Single-cell necrosis of the kidney and bladder urothelium was also noted in the chronic study. The renal changes were dose-dependent and reversible. Severe tubular degeneration/regeneration and marked glomerulonephritis as a result of immune complex disease associated with ADA led to the early euthanasia of 1 monkey following 5 weekly doses of 10 mg/kg. Increased albumin/creatinine ratio (albuminuria) as been reported in participants receiving belantamab mafodotin not indicative of disease progression and, in such cases, appropriate monitoring and dose modification should be considered.	• Kidney function monitoring, including albumin/creatinine ratio. • Education of participants on the need to maintain adequate urinary output. • Dose modification guidelines for increased serum creatinine and urinary albumin/creatinine ratio are outlined in Section 11 and Section 7.1.
Increased Infections due to Immunosuppression or Neutropenia	In nonclinical studies, belantamab mafodotin has been associated with decrease in immunoglobulins in monkeys, at all doses. An increase in immunoglobulins was seen in rats (rats are not an antigen-specific species for belantamab mafodotin).	• Participants with an active infection are excluded. • Monitoring for infections and immediate treatment of immunosuppression

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Immunosuppression is frequently associated with an increased risk of infection. Serious and non-serious infections have been reported in belantamab mafodotin studies, including respiratory infections, pneumonia, and sepsis. Neutropenic events, including febrile neutropenia have been observed with belantamab mafodotin.	according to standard practice. • Routine monitoring of hematologic panels as outlined in the SoA (Section 1.3). • Supportive therapy per local medical practice (e.g., growth factors). • Prophylactic antibiotics, per local institutional guidance, in participants with Grade 3-4 neutropenia. • Immediate hospitalization of participants with febrile neutropenia. • Dose modification guidelines are outlined in Section 11.
Infusion-Related Reactions (IRRs)	IRRs were reported in participants treated with belantamab mafodotin. Most IRRs observed to date were Grade 1 to 2 and manageable with medical treatment.	• Close monitoring for signs of IRR. • Consider premedication for IRR in participants at risk. • If an IRR occurs follow according to guidance in Section 11.
Pneumonitis	Nonclinical safety experiments have demonstrated the presence of progressive microscopic changes in the lungs (prominent alveolar macrophages associated with eosinophilic material; mixed perivascular/neutrophilic inflammation) in rats at all doses tested. Cases of pneumonitis, including fatal events, have been observed with belantamab mafodotin although a causal association has not been established.	• Monitoring for clinical signs and symptoms related to pulmonary toxicity. If a participant experiences new or worsening pulmonary symptoms, (e.g., cough, dyspnea) without obvious etiology, further diagnostic tests and management should be performed and further treatment with belantamab mafodotin delayed are detailed in Section 11. • An overall benefit/risk assessment should be considered for the participant prior to continuing belantamab mafodotin treatment.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Further diagnostic tests and management will be implemented immediately in cases of suspected pneumonitis as described in Section 6.6.4.

Note: Refer to the current version of the belantamab mafodotin IB for further information.

2.3.2. Benefit Assessment

Belantamab mafodotin has demonstrated strong single-agent activity in 2 clinical studies (FTIH) study BMA117159/DREAMM-1 and Phase 2 Study 205678/DREAMM-2) conducted in heavily pre-treated participants with RRMM (Q3W schedule via IV administration)- details of efficacy and safety findings for both studies are outlined in Section 2.2.4.

The combination treatment of belantamab mafodotin with other agents supported by scientific rationale is expected to result in improved outcomes, and to provide additional control of symptoms or disease progression. It is reasonable to hypothesize that such combination may benefit MM participants, who are refractory to currently available treatments.

2.3.3. Overall Benefit: Risk Conclusion

As of the date of publishing this protocol, there is no clinical experience with the combination of belantamab mafodotin with the investigational combination partners within each sub-study. The observed clinical activity of belantamab mafodotin [Trudel, 2019; Trudel, 2018] and the scientific rationale for the proposed combinations will suggest that the combination(s) may provide additional anti-tumor effect in participants with RRMM.

Combination treatment selection will depend on the available safety data from the studies for each monotherapy that suggest a reasonable safety profile for the combination. The sub-study benefit:risk conclusions from the known monotherapy data for each are contained within each sub-study section. If there are any potential overlapping risks with belantamab mafodotin, they will be noted here as well. Adequate monitoring, risk mitigation strategies and guidance for dose reductions/stopping criteria have been provided in the protocol to attempt to minimize anticipated risks associated with exposure to belantamab mafodotin in combination with each agent.

3. OBJECTIVES AND ENDPOINTS

The purpose of this Phase 1/2 study is to determine whether belantamab mafodotin can be safely administered in combination with anti-cancer treatments that could improve the clinical benefit of belantamab mafodotin. This will be accomplished by determining the RP2D for each treatment in combination with belantamab mafodotin (DE Phase) and determining whether a particular combination meets the safety and efficacy requirements

to be transitioned to CE. The CE Phase will then evaluate the safety and clinical activity of the selected combination(s) at selected potential RP2Ds.

The primary, key secondary, and secondary objectives, along with the corresponding endpoints for DE are listed in Table 10; while the primary, secondary, and exploratory objectives for CE are listed in Table 11.

Table 10 Objectives and Endpoints for Dose Exploration

Objectives	Endpoints
Primary	
To determine the safety and tolerability of belantamab mafodotin in combination with other anti-cancer treatments (in each sub-study), and to establish the recommended Phase 2 dose for each sub-study investigational combination treatment to explore in the CE Phase in participants with RRMM	• Percentage (number) of participants with DLTs • Percentage of participants with AEs, changes in clinical signs and laboratory parameters
Key Secondary	
To evaluate the clinical measures of efficacy of belantamab mafodotin and combination treatments in participants with RRMM	• Clinical activity measured as ORR, according to the IMWG Response Criteria [Kumar, 2016]
Secondary	
To further evaluate the clinical measures of efficacy of belantamab mafodotin and combination treatments in each sub-study in participants with RRMM	Rates of: • PR • VGPR • CR • sCR
To describe the exposure of belantamab mafodotin when administered in combination with each combination treatment within each sub-study in participants with RRMM	• Belantamab mafodotin observed concentrations
To describe the exposure of the partner anti-cancer treatment when administered in combination with belantamab mafodotin in each sub-study	• Anti-cancer combination treatment's observed concentration
To assess ADAs against belantamab mafodotin and against combination treatments (biologics) that are administered by IV infusion within each sub-study	• Incidence and titers of ADAs against belantamab mafodotin and combination treatments, when measured
To further determine the safety and tolerability of belantamab mafodotin in combination with other anti-cancer treatments (in each sub-study)	• Incidence of AEs of special interest for belantamab mafodotin • Incidence of AEs of special interest for combination treatments • Incidence of ocular findings on ophthalmic exam
Exploratory	
To evaluate the PK profile of belantamab mafodotin when administered in combination with each combination treatment within each sub-study in participants with RRMM	• Belantamab mafodotin PK parameters, as data permit
To evaluate the PK profile of the partner anti-cancer treatment when administered in combination with belantamab mafodotin	• Anti-cancer combination treatment's PK parameters, as data permit
To further explore the anti-tumor activity of belantamab mafodotin in combination with treatments in participants with RRMM	• CBR [Kumar, 2016] • TTR • OS

Objectives	Endpoints
	• PFS • DoR
To explore the relationship between clinical response and other biologic characteristics including, but not limited to, BCMA expression on tumor cells and serum sBCMA concentrations	• Assess various biomarkers at baseline and on treatment, by tumor and blood-based analysis of DNA, RNA and protein, including but not limited to evaluating baseline BCMA expression and/or immune status in tumor tissue and in the tumor microenvironment, and/or serum soluble BCMA levels, and their relationship to clinical response
To investigate pharmacogenomics in relation to belantamab mafodotin	• Evaluate the relationship between host genetic variation and response to belantamab mafodotin
To explore exposure-response relationships between belantamab mafodotin and/or combination treatment exposure and clinical endpoints	• Explore relationships between belantamab mafodotin and/or combination treatment exposure (e.g., dose, dose intensity, concentration, Cmax, or AUC) vs clinical endpoints (e.g., response, corneal event), if data permit
To assess MRD in participants who achieve VGPR or better.	• MRD negativity rate, defined as: the percentage of participants who achieve MRD negative by Next Generation Sequencing

Table 11 Objectives and Endpoints for Part 2 – Cohort Expansion

Objectives	Endpoints
Primary	
To assess the clinical activity of belantamab mafodotin at each potential RP2D in combination with anti-cancer treatments compared to belantamab mafodotin monotherapy in participants with RRMM	• ORR, according to the IMWG Response Criteria [Kumar, 2016]
Secondary	
To further assess clinical activity of combination treatments with belantamab mafodotin at each potential RP2D compared with monotherapy within each sub-study in participants with RRMM	• CBR according to the IMWG Response Criteria [Kumar, 2016] • PFS • DoR • TTR • Rates of: PR, VGPR; CR, sCR • OS
To further characterize the safety of belantamab mafodotin and belantamab mafodotin in combination with anti-cancer treatments within each sub-study in participants with RRMM	• Incidence of AEs, SAEs, AEs leading to discontinuation or dose reduction/delay, changes in clinical signs, and laboratory parameters. • Incidence of AESIs for belantamab mafodotin. • Incidence of AESIs for the individual partner for each sub-study. • Incidence of ocular findings on ophthalmic exam for belantamab mafodotin.
To evaluate plasma concentrations of belantamab mafodotin and combination treatments in participants within each sub-study with RRMM	• Belantamab mafodotin and combination treatment's plasma concentrations
To assess ADAs against belantamab mafodotin and against combination treatments (biologics) that are administered by IV infusion within each sub-study	• Incidence and titers of ADAs against belantamab mafodotin and combination treatments, when measured

Objectives	Endpoints
Exploratory	
To explore the relationship between clinical response and other biologic characteristics including, but not limited to, BCMA expression on tumor cells and sBCMA concentrations	• Assess various biomarkers, at baseline and on treatment, by tumor and blood-based analysis of DNA, RNA and protein, including but not limited to, evaluating baseline BCMA expression and/or immune status in tumor tissue and in the tumor microenvironment, and/or serum soluble BCMA levels, and their relationship to clinical response
To investigate pharmacogenomics in relation to belantamab mafodotin	• Evaluate the relationship between host genetic variation and response to belantamab mafodotin
To evaluate disease and treatment-related symptoms and impact on function and health-related quality of life	• Qualitative telephone interview(s)
To assess the self-reported symptomatic AEs by evaluation of tolerability of belantamab mafodotin in combination with anti-cancer treatments within each stub-study in participants with RRMM	• Changes from baseline in symptoms and related impacts as measured by OSDI and PRO-CTCAE
To explore the effect of each potential RP2D of belantamab mafodotin in combination treatments on health-related quality of life in participants with RRMM	• Changes from baseline in health-related quality of life as measured by the EORTC QLQ-C30 AND EORTC IL52 (disease symptoms domain of the EORTC QLQ-MY20)
To evaluate the PK profile of belantamab mafodotin and combination treatments in participants with RRMM	• Belantamab mafodotin and combination treatments PK parameters, as data permit
To explore exposure-response relationships between belantamab mafodotin and/or combination treatment exposure and clinical endpoints	• Explore relationships between belantamab mafodotin and/or combination treatment exposure (e.g., dose, dose intensity, concentration, Cmax, or AUC) vs clinical endpoints (e.g., response, corneal event), if data permit
To assess MRD in participants who achieve VGPR or better	• MRD negativity rate, defined as: the percentage of participants who achieve MRD negative by Next Generation Sequencing

4. STUDY DESIGN

4.1. Overall Design

The platform design is an efficient tool incorporating a single MP, wherein, multiple treatment combinations will be evaluated in separate sub-studies. Each sub-study is defined as the data collected in DE and CE for each combination treatment arm and its associated shared control arm (in CE only) within Study 208887.

There is a DE Phase which will evaluate the safety and tolerability profile of belantamab mafodotin when administered in combination with other anti-cancer treatments. The number of dose levels explored will vary per sub-study, and up to 15 participants per dose level will be evaluated for safety and preliminary efficacy. One or more potential RP2Ds for each combination treatment could be identified based on the safety and preliminary efficacy in DE.

Where appropriate, these will be followed by a CE Phase which will evaluate the clinical activity of the combination treatment in comparison to monotherapy belantamab mafodotin, the shared control arm, and additional participants at each potential RP2D for each sub-study. The decision whether to initiate CE for a given combination/dose level will be based on the totality of the data, at the sponsor's discretion, including safety, efficacy, tolerability, PK, and pharmacodynamics.

- At the start of the first CE Phase, participants will initially be randomized 1:1 within that sub-study CE to either the investigational combination treatment or a shared monotherapy belantamab mafodotin control arm, until 35 participants have been assigned to the combination treatment arm. As new sub-studies are added to the study or closed during the trial, the randomization ratio will be adjusted if >35 participants have been randomized to the shared belantamab mafodotin control arm (see Table 14).
- The first interim analysis will be conducted when at least 10 CE combination treatment participants are evaluable. A second interim analysis may be performed when approximately 18 combination treatment participants are evaluable. Participants are considered evaluable if they have progressed/died, discontinued study treatment, or have had 3 post-baseline efficacy assessments or at least 2 planned doses.

The platform design allows for the introduction of new sub-studies, with either the shared control or potentially different control arms, as treatment paradigms evolve. The combination agents for each sub-study of this platform design will be chosen based on scientific rationale and/or available preclinical data. This will lead to generation of robust statistical data in the CE Phase to inform future studies. Detailed information for each sub-study is provided in the respective sub-study protocol sections.

The primary analysis in CE will be performed when all participants in the CE Phase have been followed at least 6 months, have progressed/died or discontinued study treatment. The final analysis will be performed at the end of each sub-study. See Schema in Section 1.2 for the general design schemas for the platform study.

4.1.1. Dose Exploration Phase

The DE is designed to evaluate safety, tolerability, and clinical activity, as well as selecting one or more potential RP2Ds for each sub-study investigational treatment combination. The dose exploration phase will consist of a starting dose (SD) cohort for all sub-studies. This SD is dependent on the efficacy and safety findings from previous monotherapy studies of belantamab mafodotin and the specific therapy to be combined with belantamab mafodotin. Sub-studies may additionally involve 1 or more dose-escalation cohort(s), or de-escalation cohort(s).

A mTPI [Ji, 2010] method will be used to guide dose escalation/de-escalation decisions (see Section 4.1.1.2., below). Unless otherwise specified in the sub-study, an evaluation of the available safety data over the first cycle of treatment f is required from at least 3 participants before a decision is made to enroll additional participants at the same, or the subsequent dose level based on the mTPI algorithm (Table 13). The decisions will occur following review of these data and joint discussion by the GSK SRT and investigators. Membership, roles and accountabilities, and the process for safety review and meeting frequency is outlined in the Dose Escalation Plan.

Cohort 1; Starting Doses belantamab mafodotin + combination treatment: This will involve the administration of the Starting Dose to 3 participants, starting with a sentinel participant. Provided there are no AEs fulfilling DLT criteria in the sentinel participant, the second participant will be dosed at least 7 days later, followed by the third participant who will be dosed at least 3 days after the second participant. If the safety profile in the first 3 participants is deemed to be favorable by the SRT, then as per the mTPI the dose recommendation for the next cohort will be considered by the SRT (see Figure 3).

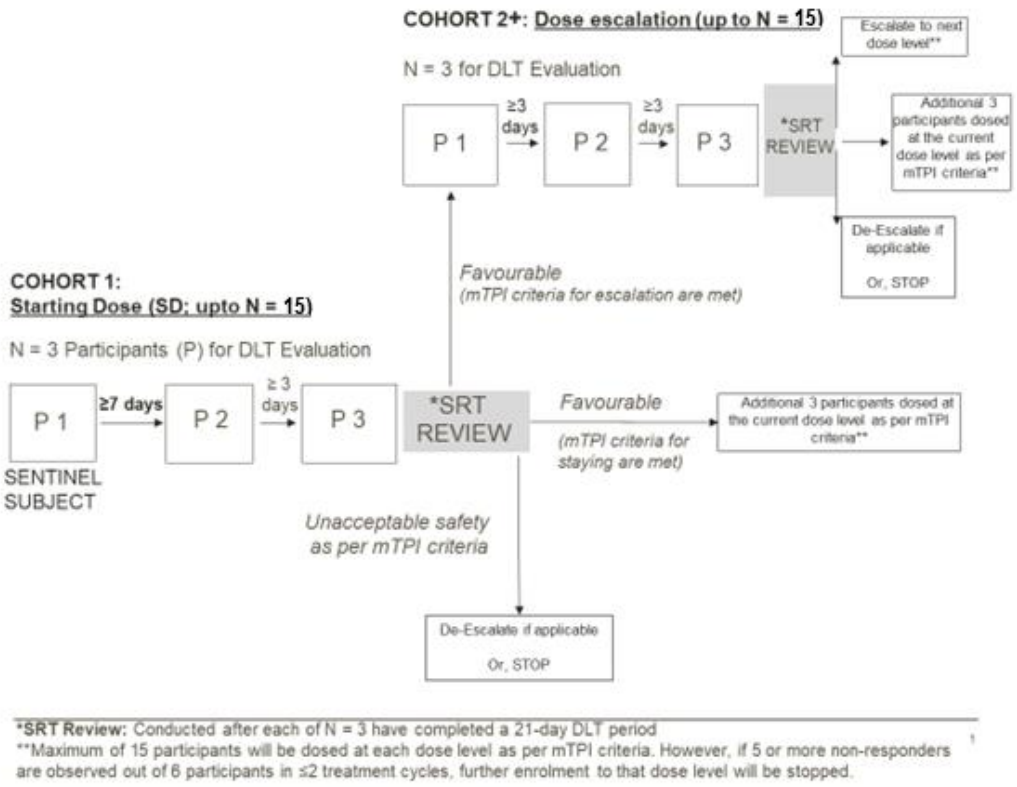
Cohort 2+; Dose Escalation: This may involve the administration of 1 or more escalating dose levels. Unless otherwise specified in the sub-study, each dose escalation cohort will consist of at least 3 participants, and up to 15 participants. To minimize the risk of inadvertently exceeding the MTD in multiple participants, the first 3 participants in any dose escalation cohort will be dosed with an interval of at least 3 days between participants. If the safety profile in these first 3 participants in the dose escalation cohort is deemed to be favorable by the SRT, then a maximum of 15 participants will be dosed at any given dose level as per mTPI criteria. However, if 5 or more non-responders are observed out of 6 participants in ≤2 treatment cycles, further enrolment to that dose level will be stopped. Dose escalation will also be considered by the SRT and the DRC (see Figure 3).

Dose De-escalation: Dependent on the specific sub-study, there may be an option to de-escalate the dose of the combination treatment (see Figure 3 and individual sub-study sections) from the SD after agreement of the SRT.

For Cohort 1 and Cohort 2+ above, if a decision is made to escalate to a higher dose, the current dose may continue to expand as per mTPI algorithm up to 15 participants. Subsequent decision(s) to escalate, stay, or de-escalate will be guided by the mTPI algorithm and will also take into consideration the totality of available DLT data from all dose cohorts. Additional details are provided in Section 4.1.1.2.

The sponsor may decide not to evaluate all dose levels based on data external to this study.

Figure 3 Inter-participant dosing schematic and mTPI-guided safety pathway to expansion of starting dose cohort, + / - triggering of dose escalation(s), or dose de-escalation(s)



*SRT Review: Conducted after each of N = 3 have completed a 21-day DLT period
**Maximum of 15 participants will be dosed at each dose level as per mTPI criteria. However, if 5 or more non-responders are observed out of 6 participants in ≤2 treatment cycles, further enrolment to that dose level will be stopped.

4.1.1.1. Dose-Limiting-Toxicity

An AE is considered as a DLT if any of the following criteria in Table 12 are fulfilled, unless the AE is unequivocally associated with the underlying disease, medical comorbidities, and/or specific exceptions.

Table 12 DLT Criteria for Dose Escalation

Criteria for Identification of DLTs in the DE Phase Cycle 1 (for length of cycle see specific sub-study)	
Toxicity Type	DLT Definition and Grade
Hematologic	• Grade 3, 4, and 5 febrile neutropenia of any duration (ANC <1000/mm^3 with a single temperature of >38.3° C [101°F], or a sustained temperature of ≥38°C [100.4°F] for more than 1 hour as per NCI-CTCAE [Version 5.0]). • Grade 3, 4, and 5 thrombocytopenia accompanied by clinically significant bleeding.
Non-hematologic, excluding corneal toxicity	Any Grade 3 or greater non-hematologic laboratory value if: • The laboratory abnormality persists for >48 h despite supportive treatment, and; • The abnormality leads to hospitalization. Grade 3, 4 and 5 toxicity Exceptions:

	• Grade 3 or 4 nausea, vomiting, or diarrhea that can be controlled using symptomatic treatment. • Grade 3 hypertension (controlled following addition of up to 2 anti-hypertensive medications). • Events and abnormalities which are unequivocally related to progression of underlying disease or comorbidities. • Grade 3 or 4 TLS, successfully managed clinically and resolves within 7 days without end-organ damage. • Grade 3 or 4 IRR which does resolves with appropriate supportive treatment within 48 h.
Corneal events	Grade 4 per the KVA scale (Table 19).
Other organ specific toxicities	Liver toxicity, or other organ toxicity meeting prespecified GSK stopping criteria.
List of most frequent AEs for belantamab mafodotin provided in the Study Reference Manual	

AEs including those observed before DLT evaluation period may be considered as DLT depending on the individual case at the DE meeting regardless of DLT criteria.

4.1.1.2. mTPI in Dose Exploration

For each sub-study, data considered for RP2D selection will include, but not be limited to: safety, available PK profile, and observed signs of clinical activity. The RP2D may be the MTD, or a lower dose that provides adequate PK properties and clinical activity with acceptable tolerability of a combination treatment. Lower doses than those described in the protocol may be utilized based on review of available data.

A mTPI design will be implemented to aid dose escalation decisions (Table 13) [Ji, 2010]. An initial cohort of 3 participants will be recruited in DE as a starting dose level within a sub-study. If the dose is safe based on these 3 participants, up to an additional 12 participants may be enrolled in this dose level and decision to dose-escalate could be made. If it is not safe, 3 participants will be enrolled in a de-escalated dose or the dose level will be terminated. Dose exploration will be guided by mTPI principles.

The design assumes (i) up to 15 participants will complete the dose exploration period per dose combination level, (ii) the target true underlying toxicity rate for each treatment combination falls within the range from 20% to 30% and centered at 25%, and iii) a dose will be determined to be unacceptably toxic if there is >95% probability that the toxicity rate is higher than the target range. For the current dose level, monitoring rules guiding dose exploration are provided (Table 13). Columns provide the numbers of participants treated at the current dose level, and rows provide the corresponding numbers of participants experiencing toxicity. The entries of the table are dose-finding decisions (ie, E, S, and D) representing escalating the dose, staying at the same dose, and de-escalating the dose. In addition, decision U means that the current dose level is unacceptable because of high toxicity and should be excluded from the study. For example, when 1 of 3 participants experience toxicity, the decision can be located at row 1 and column 3, which is S - to stay at the current dose level. Consequently, the next cohort of participants will be treated at the same dose level currently being used. If 0 of 3 participants experience toxicity, the decision is at row 0 and column 3, which is E- to escalate. Thus, the next cohort of participants may be treated at the next higher dose level. If 3 of 3 participants experience toxicity, the decision is DU- to de-escalate to the next lower

dose level and exclude the current dose from the trial, because the high toxicity level is unacceptable.

Table 13 Dose-Finding Spreadsheet of the Modified Toxicity Probability Interval (mTPI) Method

		Number of patients treated at current dose														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Number of DLTS	0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
	1	D	D	S	S	S	S	E	E	E	E	E	E	E	E	E
	2		DU	D	D	S	S	S	S	S	S	S	S	S	E	E
	3			DU	DU	DU	D	S	S	S	S	S	S	S	S	S
	4				DU	DU	DU	DU	DU	D	S	S	S	S	S	S
	5					DU	DU	DU	DU	DU	DU	D	S	S	S	S
	6						DU	DU	DU	DU	DU	DU	DU	DU	D	S
	7							DU	DU	DU	DU	DU	DU	DU	DU	DU
	8								DU	DU	DU	DU	DU	DU	DU	DU
	9									DU	DU	DU	DU	DU	DU	DU
	10										DU	DU	DU	DU	DU	DU
	11											DU	DU	DU	DU	DU
	12												DU	DU	DU	DU
	13													DU	DU	DU
	14														DU	DU
	15															DU

1. E = Escalate to the next higher dose.
2. S = Stay at the current dose.
3. D = De-escalate to the next lower dose.
4. U = The current dose is unacceptably toxic.
5. MTD = 25%.
6. Epsilon 1 = 0.05.
7. Epsilon 2 = 0.05.

The decision criteria in the mTPI Table will continue to apply to all cohorts that continue to recruit participants. If emerging DLT data in a lower dose cohort result in either the decision S or D as per mTPI algorithm, then recruitment in higher dose cohorts could be paused. A review of all available relevant data will be conducted by SRT. The SRT will recommend the next steps based on totality of available data.

An IA will be performed for each sub-study combination treatment at the end of the DE Phase using safety, PK, and efficacy data. A minimum of 2 responders and ≥20% response rate from a maximum of 15 participants enrolled at a particular dose level will be needed to transition into the CE Phase of each sub-study (Figure 1). However, the decision to move to the CE Phase is based on the totality of available data. The IA will be performed when up to 15 participants have been treated where appropriate per dose level and have undergone 3 efficacy assessments (1 baseline and 2 post-baseline assessments) or have discontinued study therapy due to confirmed progression, death, or study therapy related toxicity. The dose decisions of each RP2D will be based on the totality of the

clinical safety assessment, including but not limited to, DLTs, AEs that are not DLTs, laboratory, PK, and efficacy.

4.1.2. Cohort Expansion Phase

Once a sub-study transitions through the DE Phase, participants may be enrolled in the CE Phase at each potential RP2D of the combination treatment of the sub-study to further assess the additional clinical benefit and safety of that combination. In the CE Phase, randomization will be utilized to assign participants to and within a sub-study; that is participants will be randomized to a sub-study, and within a sub-study to either the combination treatment or the belantamab mafodotin monotherapy control arm (Figure 1). Data from the control arm will be shared across all sub-studies unless otherwise specified in the sub-study protocol. The 2.5 mg/kg Q3W dose of belantamab mafodotin will be used in the control arm on the basis of results from DREAMM-2 [Lonial, 2020]. Randomization within a sub-study will also be stratified by the number of prior lines of therapy (3-4 vs >4).

Detailed information for each individual combination is provided in the respective sub-study protocol.

As described above, the study design allows for the addition of new sub-studies or CEs within a sub-study. These will be added via amendments. As new sub-studies or CEs within a sub-study are added to the study or closed during the study, the randomization ratio will be amended if >35 participants have been randomized to the shared belantamab mafodotin control arm (Table 14).

Table 14 Randomization Ratio and Proportion of Participants Randomized to the Monotherapy Arm When There Are Concurrent Arms (CE only)

CEs	Randomization Ratio* between each combination and control (Proportion of participants randomized to belantamab mafodotin control arm)	
	≤35th participants	>35th participants
1 CE and the monotherapy control	1:1 (50%)	2:1 (33%)
2 CEs and the monotherapy control	1:1 (33%)	2:1 (20%)
3 CEs and the monotherapy control	1:1 (25%)	2:1 (14%)
4 CEs and the monotherapy control	1:1 (20%)	2:1 (11%)
5 CEs and the monotherapy control	1:1 (17%)	2:1 (9%)
6 CEs and the monotherapy control	1:1 (14%)	2:1 (8%)
7 CEs and the monotherapy control	1:1 (13%)	2:1 (7%)
8 CEs and the monotherapy control	1:1 (11%)	2:1 (6%)

* Randomization ratio refers to the overall ratio of # of participants in each combination arm relative to monotherapy (e.g., when 2 CEs are open, then the ratio 1:1 means 1[CE1 combination]:1[CE2 combination]:1[monotherapy]).

Within each sub-study, the belantamab mafodotin monotherapy control arm will be compared to a combination belantamab mafodotin treatment. A combination treatment will be considered superior to belantamab mafodotin monotherapy in ORR if the posterior probability of the response rate in combination being greater than the response rate in belantamab mafodotin monotherapy is at least 90%. Within this Bayesian framework, a robust mixture prior [Schmidli, 2014] will be used to combine historical

data on ORR from DREAMM-2 (205678) with data accrued on the belantamab mafodotin monotherapy arm in this study.

The first interim analysis will be conducted when at least 10 CE combination treatment participants are evaluable. A second interim analysis may be performed when approximately 18 combination treatment participants are evaluable. Participants are considered evaluable if they have progressed/died, discontinued study treatment, or have had 3 post-baseline efficacy assessments or at least 2 planned doses.

Participants will be treated until confirmed disease progression, unacceptable toxicity, withdrawal of consent or death.

Participants who discontinue study treatment for reasons other than disease progression will enter the Follow-up period for PFS assessment during which they will be followed per SoA until disease progression.

After confirmed disease progression, all participants will be followed for OS until death or the end of study.

4.1.3. Number of Participants per Sub-Study

Approximately 85 participants per sub-study combination treatment will be enrolled in the DE and CE Phases, although this will vary based on the number of dose levels in the DE Phase and number of doses selected for CE. Up to 15 DLT evaluable participants per dose level will be evaluated during the DE Phase. The number of dose levels studied will be determined for each sub-study.

4.2. Scientific Rationale for Study Design

The platform design is an efficient tool incorporating a single MP, wherein multiple treatment combinations, as sub-studies, will be evaluated simultaneously. A sub-study combination treatment will be individually assessed for safety and dose in DE and for safety and efficacy in CE. In CE, each sub-study participant will be randomized to the sub-study combination treatment vs control. The control arm will consist of belantamab mafodotin monotherapy. Scientific rationales for each sub-study can be found in the respective sub-study protocol section.

4.3. Justification for Starting Dose of Belantamab Mafodotin

The starting dose for belantamab mafodotin in Study 208887 (unless specified differently in a sub-study) will be 1.9 mg/kg Q3W in combination with other anti-cancer treatments. The justification for selecting the 1.9 mg/kg Q3W is as follows:

1) The 1.9 mg/kg Q3W dose is 1 dose level lower than the currently selected based on the results from DREAMM-2 in participants with RRMM.
2) Following administration of 1.9 mg/kg Q3W in the FTIH monotherapy study (BMA117159), target engagement was greater than 90% at the end of the first infusion based on decrease in plasma free sBCMA from baseline.

3) Based on the Bayesian logistic regression modelling of efficacy data in the FTIH monotherapy study (BMA117159 – 26 June 2017 cutoff), the 1.9 mg/kg Q3W dose has a response that is lower than at 2.5 mg/kg (predicted response rate 25.3% with a 95% credible interval of 9.4% and 42.2%); therefore, a dose lower than 1.9 mg/kg Q3W is considered not suitable as a starting dose.

Dose justification for each combination partner dose level can be found in the respective subsections.

4.4. Participant Completion and End of Study Definitions

A participant is considered to have completed the study if they received at least 1 cycle of combination study treatment, and the participant is followed until death (even after starting a new anti-cancer treatment), withdrawn consent, is lost to follow-up, or until the end of the sub-study.

If a sub-study meets efficacy criteria defined in Section 9.4, participants may be followed for PFS and OS for up to 36 months.

A sub-study may close after or during DE for safety or tolerability reasons or at the discretion of the Sponsor. Those participants still benefiting from study drug, in the opinion of their treating physician, may continue to receive study treatment.

The EoS is the last visit of the last participant in the last sub-study.

5. STUDY POPULATION

The study will enroll adult participants with RRMM, who have been previously treated with at least 3 prior lines that include the following: an immunomodulatory drug, PI and an anti-CD38 monoclonal antibody treatment. Lines of therapy are defined by consensus panel of the IMWG [Rajkumar, 2011]. Approximately 85 participants per sub-study will be enrolled across the DE and CE Phases.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria for All Participants

Participants are eligible to be included in the study only if all of the criteria in Section 5.1 and Section 5.2 apply. In addition, participants must fulfill additional inclusion/exclusion criteria for at least 1 partner combination sub-study. Criteria for each individual sub-study can be found in the respective sub-study protocol section.

Age

1. Participant must be 18 years of age inclusive or older, at the time of signing the informed consent. **Note:** if country/site age requirements for consent differ, the more stringent (e.g., higher age) restriction will be required for that country/site.

Type of Participant and Disease Characteristics

2. Participants who have histologically or cytologically confirmed diagnosis of MM, as defined by the International Myeloma Working Group (IMWG, [Rajkumar, 2014]).
3. Participants who have been treated with at least 3 prior lines of anti-myeloma treatments including an immunomodulating agent (eg. lenalidomide), a proteasome inhibitor (eg. bortezomib) and an anti-CD38 monoclonal antibody. Lines of therapy are defined by consensus panel of the International Myeloma Workshop [Rajkumar, 2011].
4. Participants with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:
    a. transplant was >100 days prior to Screening.
    b. no active infection(s).
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, unless ECOG ≤2 is due solely to skeletal complications and/or skeletal pain due to MM.
6. Measurable disease defined as at least 1 of the following:
    - Serum M-protein ≥0.5 g/dL (≥5 g/L).
    - Urine M-protein ≥200 mg/24 hours.
    - Serum free light chain (FLC) assay: Involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65).
7. Have organ system functions as defined by the laboratory assessments in Table 15:

Table 15 Adequate Organ System Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.0 x10^9/L
Hemoglobin	≥8.0 g/dL
Platelets	≥50 x10^9/L
Hepatic	
Total bilirubin	≤1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
Alanine transaminase (ALT) Aspartate aminotransferase (AST)	<2.5xULN <2.5xULN
Renal	
Estimated glomerular filtration rate (eGFR)[1] Spot urine (albumin/creatinine ratio)	≥30 mL/min/1.73 m^2 <500 mg/g (56 mg/mmol)

1. As calculated by Modified Diet in Renal Disease (MDRD) formula (Appendix 6).

8. Participants who have tested positive for HBcAb can be enrolled if the following criteria are met:

Serology result	Screening	During Study Treatment
HBcAb+, HBsAg-	HBV-DNA undetectable	Monitoring per protocol (Section 6.6.5). Initiating antiviral treatment if HBV-DNA becomes detectable.

9. All prior treatment-related toxicities (defined by National Cancer Institute-Common Toxicity Criteria for Adverse Events [NCI-CTCAE], Version 5.0, 2017) must be Grade ≤1 at the time of Screening except for alopecia (any Grade), neuropathy (Grade ≤2), or endocrinopathy managed with replacement therapy (any Grade).
10. Participants who are currently receiving physiological doses oral steroids (<10 mg/day), inhaled steroids or ophthalmological steroids are allowed on study.

Sex

11. Male or female.

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies (see Appendix 7 for further details).

a. Male Participants:

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in the clinical studies.

Male participants are eligible to participate if they agree to the following during the treatment period and for at least 6 months after the last dose of study treatment to allow for clearance of any altered sperm:

Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception/barrier as detailed below
- Agree to use a male condom, even if they have undergone a successful vasectomy, and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year when having sexual intercourse with a woman of childbearing potential who is not currently pregnant. Male participants should also use a condom when having sexual intercourse with pregnant females.

b. Female Participants:

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP)

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 7 during the treatment period and for 4 months after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
- A WOCBP must have a negative highly sensitive pregnancy test [urine or serum] as required by local regulations within 72 hours before the first dose of study treatment.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

12. Participants or legally authorized representative (LAR) sign written informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Note: Use of LAR is not applicable for Germany.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Symptomatic amyloidosis, active 'polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes' (POEMS) syndrome, current or past diagnosis of plasma cell leukemia, as per 2021 IMWG guidelines (Fernández de Larrea et al 2021).
2. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions (including lab abnormalities) that could interfere with participants safety, obtaining informed consent, or compliance with study procedures.
3. Current corneal epithelial disease except mild punctate keratopathy.

4. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. Note: Stable chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if participant otherwise meets entry criteria.
5. Malignancies other than disease under study are excluded, except for any other malignancy from which the participant has been disease-free for more than 2 years and, in the opinion of the principal investigators and Medical Director, will not affect the evaluation of the effects of this clinical study treatment on the currently targeted malignancy (MM).
    - Participants with curatively treated non-melanoma skin cancer are not excluded.
6. Evidence of cardiovascular risk including any of the following:
    a. Evidence of current clinically significant untreated arrhythmias, including clinically significant ECG abnormalities such as second degree (Mobiz Type II) or third degree atrioventricular (AV) block;
    b. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, stenting or bypass grafting, all within 3 months of Screening;
    c. Class III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system;
    d. Uncontrolled hypertension.
7. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to belantamab mafodotin or any of the components of the study treatment. History of severe hypersensitivity to other mAbs.
8. Active infection requiring antibiotic, antiviral, or antifungal treatment.
9. Known HIV infection, unless the participant can meet **all** the following criteria:
    - Established anti-retroviral therapy for at least 4 weeks and HIV viral load <400 copies/mL
    - CD4+ T-cell (CD4+) counts ≥350 cells/uL
    - No history of AIDS-defining opportunistic infections within the last 12 months

    Note: consideration must be given to anti-retroviral therapy and prophylactic antimicrobials that may have a drug:drug interaction and/or overlapping toxicities with belantamab mafodotin or other combination products as relevant (see Section 6.5.2).
10. Recent history (within the past 6 months) of acute diverticulitis, inflammatory bowel disease, intra-abdominal abscess, or gastrointestinal obstruction.
11. Presence of hepatitis B surface antigen (HBsAg) at Screening or within prior history.
12. Positive hepatitis C antibody test result or positive hepatitis C RNA test result at Screening or within 3 months prior to first dose of study treatment.

Note: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if confirmatory negative Hepatitis C RNA test is obtained. Hepatitis RNA testing is optional and participants with negative Hepatitis C antibody test are not required to undergo Hepatitis C RNA testing.

13. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect participants safety). Participants with isolated proteinuria resulting from MM are eligible, provided they fulfill criteria given in Table 15.

Prior/Concomitant Therapy

14. Participants who have received prior therapy with belantamab mafodotin are excluded. Participants previously treated with other BCMA-targeting agents, such as CAR-T cells or bispecific antibodies, are permitted only during the DE Phase.
15. Other monoclonal antibodies within 30 days or systemic anti-myeloma therapy within <14 days of first dose of study drug.
16. Prior radiotherapy within 2 weeks of start of study therapy. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system (CNS) disease.
17. Plasmapheresis within 7 days prior to the first dose of study drug.
18. Prior allogeneic transplant is prohibited.
19. Participants who have received prior CAR-T therapy with lymphodepletion with chemotherapy within 3 months of Screening.
20. Any major surgery (other than bone-stabilizing surgery) within 30 days of first dose.
21. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drugs, or treatment with an investigational agent or approved systemic anti-myeloma therapy (including systemic steroids) within 14 days or 5 half-lives of receiving the first dose of study drugs, whichever is shorter.

Other Exclusions

22. Pregnant or lactating female.
23. Has received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony stimulating factor [GM-CSF], recombinant erythropoietin) or any thrombopoietin receptor agonists within 2 weeks before the first dose of study drug.
24. Participants must not receive live/live attenuated vaccines within 30 days prior to first dose of study treatment or whilst receiving belantamab mafodotin ±partner agent in any sub-study arm of the platform study. Examples of live vaccines include, but are not limited to the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza and SARS-CoV-2 vaccines for injection are not live or attenuated virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist) are live attenuated vaccines and are not allowed.

25. Known, current drug or alcohol abuse.
26. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this study, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific participant.

5.3. Lifestyle Considerations

Directions below pertain to belantamab mafodotin treatment in the study. Reference to each partner section for any additional details or modifications.

- Contact lenses are prohibited while the participant is on study. Following discontinuation of belantamab mafodotin treatment, contact lens use may be restarted after the qualified eye care specialist (see Appendix 10) confirms there are no other contraindications. Use of bandage contact lenses is permitted during study treatment as directed by the treating eye care specialist.
- Participants must not receive live/live attenuated vaccines while receiving belantamab mafodotin ± partner agent in any sub-study of the platform study and for at least 70 days following last study treatment. Questions regarding vaccines against SARS-CoV-2 may be addressed with the Medical Director.

  During the study follow-up period, after administration of investigational agent(s) has ceased, it will be according to the investigator's judgment whether administration of a live/live attenuated vaccine is permissible based on the emerging clinical condition of the participant at the time.

5.3.1. Meals and Dietary Restrictions

There are no recognized dietary restrictions for the individual components of each study treatment.

5.3.2. Caffeine, Alcohol, and Tobacco

No restriction.

5.3.3. Activity

No restriction.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to a sub-study, or were assigned but did not receive study treatment because they did not satisfy all the Inclusion/Exclusion criteria provided (Section 5.1 and Section 5.2; see sub-study protocol sections). A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes the participant ID number,

demography, screen failure details, eligibility criteria, any SAEs, and protocol deviation, if any.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the failure was based on an element of eligibility that may change, e.g., laboratory test results. Rescreened participants should be assigned a different participant number from that assigned for the initial Screening. Refer to Section 1.3 for applicable windows for Screening procedures.

6. STUDY TREATMENT

Study treatment is defined as belantamab mafodotin administered with the sub-study-specific anti-cancer combination partner treatment and administered to a study participant according to the study protocol.

6.1. Study Treatment(s) Administered

Specifications for belantamab mafodotin treatment in this study are given in Table 16. Dose levels and de-escalation guidelines for each sub-study are given in the respective sub-study protocol section.

Table 16 Belantamab Mafodotin Study Treatment Information

Treatment Name	Belantamab mafodotin
Type	Drug
Dose Formulation	Lyophilized powder for solution for infusion
Unit Dose Strength(s)	100 mg/vial
Route of Administration	Delivered as IV solution and infused over 30-60 minutes
Dosing instructions	Reconstitute belantamab mafodotin for Injection, 100 mg with 2.0 mL of sterile WFI, dilute with saline before use. Dilute GSK2857916 in normal 0.9% saline to the appropriate concentration for the dose. Doses of GSK2857916 are to be administrated as an IV infusion via an infusion pump. See Investigator's Brochure for compatible administration materials GSK2857916 IB (GlaxoSmithKline Document Number GSK2857916. Investigator's Brochure V11, 2023).
IMP	GSK2857916 (belantamab mafodotin)
Sourcing	GSK
Packaging and Labeling	Study Treatment will be provided in vials. Each vial will be labeled as required per country requirement.

6.2. Belantamab Mafodotin Dose Administration

Belantamab mafodotin will be administered to participants intravenously as mg/kg calculated dose at the study site. The dose to be administered is based on actual body weight calculation and may be reduced for toxicity according to protocol guidelines.

For dosing, belantamab mafodotin will be administered first in the clinic on Day 1 of each cycle as a 30 to 60 minute infusion, followed by a 1 hour rest period.

Administration will be documented in the source documents (Appendix 1, Section 12.1.8) and reported in the eCRF. The time of start and end of infusion will be documented in the eCRF.

The intended cycle time of belantamab mafodotin as a monotherapy is every 21 days (+3 day window) and cannot occur sooner/more frequently than this (subsequent, consecutive dosing of belantamab mafodotin must be administered a minimum of 21 days from prior/last dose given). If in the judgment of the investigator, treatment needs to be initiated prior to the next planned scheduled dose *following a dosing delay and where clinical toxicity has resolved*, request should be discussed with the Medical Director.

The cycle of belantamab mafodotin in combination with partner drugs will be described in each sub-study section. After the infusion of belantamab mafodotin has been completed, the participant will be required to enter at least 1-hour rest period before starting a partner drug infusion where appropriate.

For oral combination therapy: oral combination therapy will be administered as directed in the sub-study protocol. The first dose should be administered ~1 hour before belantamab mafodotin (unless otherwise specified in the sub-study protocol sections), which will be infused over 30-60 minutes in both monotherapy and combination therapy. Premedication is not required prior to infusion unless deemed medically necessary by the investigator, in which case it should be administered according to institutional recommendations. In case of IRRs related to belantamab mafodotin the rules outlined in Section 7.1.3 and in Section 11 should be followed.

6.3. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Director and/or GSK study contact.

- A MSDS describing occupational hazards and recommended handling precautions will be provided to all investigators. Precaution will be taken to avoid direct contact with the study treatment. A MSDS describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Director and/or GSK study contact.
- Each study treatment (monotherapy or combination) will be intravenously administered (unless otherwise specified within a sub-study) to participants at the site. Administration will be documented in the source documents (Appendix 1, Section 12.1.8) and reported in the eCRF. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.
- Please refer to the Pharmacy Manual for additional details on preparation/handling/storage/accountability.

6.4. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. When both DE and CE are open, participants will be prioritized to the DE Phase or CE Phase. In DE, participants will be assigned to available treatment slots by a predetermined algorithmic approach. In CE, participants will be randomized to 1 of the open sub-study CEs for which they meet the eligibility criteria. Within a sub-study, participants will be randomized between the combination treatment or a shared belantamab mafodotin monotherapy arm, with randomized treatment allocation stratified by the number of prior lines of therapy.

6.5. Concomitant Therapy

Participants will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until EOT. Concomitant medications administered for/in conjunction with SAEs/AESIs after the EOT should be recorded as defined in Section 8.3.

Any concomitant medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study treatment must be recorded along with:

- Reason for use;
- Dates of administration including start and end dates;
- Prescription/administration information including dose and frequency.

The Medical Director should be contacted if there are any questions regarding concomitant or prior therapies.

6.5.1. Permitted Concomitant Medications and Therapies

Participants should receive full supportive care during the study, including transfusions, growth factors, and treatment with antibiotics, anti-emetics, antidiarrheals, and analgesics, as appropriate.

Blood product transfusions should not be administered on same day as study drug dosing.

Systemic corticosteroids are permitted in certain circumstances. See Section 6.5.2 for further details.

Concomitant therapy with bisphosphonates is allowed.

Concomitant prophylactic treatment for TLS (according to local standards) in participants with high tumor load should be considered. Participants may receive local irradiation for pain or stability control. Appropriate imaging should be performed to establish the presence of new lesions, which would constitute disease progression.

Surgery is permitted on a case-by-case basis in consultation with the Medical Director.

Use of monoclonal antibodies for serious conditions unrelated to multiple myeloma, such as SARS-CoV-2, may be permitted after consultation with the Medical Director.

Several permitted concomitant medications may need special monitoring if used. Please refer to the SRM for details.

6.5.2. Prohibited Concomitant Medications and Non-Drug Therapies

Chronic treatment with oral steroids other than part of the study treatment is prohibited while the participant is on study with the exceptions below:

- Physiological dose of steroid (ie,<10 mg/day prednisone).
- Any course of steroids (PO or IV) is permitted to treat AEs as per local standard of care.
- Steroids may be used to treat IRRs.
- Inhaled steroids are allowed.
- Short Treatment with oral steroids (≤7 days) is permitted for treatment of acute complications related to study treatment, or premedication prior to belantamab mafodotin infusion.
- Topical ophthalmic corticosteroids, such as prednisolone acetate are permitted at the ophthalmologist's discretion.

The following medications are prohibited before the first dose of study treatment (refer to Exclusion Criteria in Section 5.2 for specific time requirements) until after the last dose of study treatment is given:

- Anti-cancer therapies other than those referred to as Study Treatment that include, but are not limited to chemotherapy, immunotherapy, biologic therapy,

hormonal therapy (other than physiologic replacement), surgery, and radiation therapy (other than palliative treatment as stated in Section 6.5.1).

- Any investigational drug(s) other than those referred to as Study Treatment (belantamab mafodotin or combination partners).
- Live and live attenuated vaccines:
  - Participants must not receive live/live attenuated vaccines while receiving belantamab mafodotin ±partner agent in any sub-study arm of the platform study and for at least 70 days following last study treatment.
  - During the study follow-up period, after administration of investigational agent(s) has ceased, it will be according to the investigator's judgment whether administration of a live/live attenuated vaccine is permissible based on the emerging clinical condition of the participant at the time.
- Systemic treatment with high dose steroids within 14 days prior to C1D1.

A list of Prohibited Concomitant Medications is provided in the SRM, based on known interactions or characteristics of each component of the study treatment.

Elimination pathways for belantamab mafodotin and cys-mcMMAF have not been characterized in humans. Cys-mcMMAF was not an inhibitor, an inducer, or a good substrate of cytochrome P450 enzymes in vitro. However, cys-mcMMAF was shown to be a substrate of Pgp and organic anion transporting polypeptide (OATP1B1 and OATP1B3) in vitro. Caution should be exercised when belantamab mafodotin is combined with strong inhibitors of Pgp, and strong inhibitors of OATP should be avoided unless considered medically necessary.

For participants receiving anti-HIV and anti-microbials:

- Anti-HIV and anti-microbials that are OATP inhibitors (list provided below, full list provided in pharmacy manual) are thus prohibited unless considered medically necessary. Preferably, alternative antimicrobials and anti-HIV drugs would need to be prescribed to these participants.
- OATP inhibitors: Prohibited unless considered medically necessary
  - Anti-HIV drugs: atazanavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
  - Anti-HCV drugs: simeprevir, telaprevir
  - Antibiotic drugs: clarithromycin, erythromycin, rifampin/rifampicin

6.6. Dose Modification

Dose modification text and guidance for belantamab mafodotin is provided in this section. Please see Section 4.3 Justification for maximum starting dose of belantamab mafodotin. Also see Section 11 for guidance on guidelines for dose modification and management of events for belantamab mafodotin and other partner combination

treatments. Additional guidance for dose modification for belantamab mafodotin and other partner combination treatments is also found in Section 6.6 of each sub-study protocol.

6.6.1. Belantamab Mafodotin Dose Adjustments Due to Body Weight

The actual body weight in kg at baseline (assessed on Cycle 1 Day 1 prior to dosing) will be used for dose calculation of belantamab mafodotin in all participants during the treatment period. If the change of body weight (increase or decrease) is greater than 10%, the dose should be re-calculated based on the actual body weight at the time of dosing and thereafter will serve as the new baseline for weight comparison at subsequent visits. Participants must be weighed prior to dosing for each cycle.

6.6.2. Belantamab Mafodotin Dose Modification in DE

Doses of belantamab mafodotin higher than 2.5 mg/kg IV will not be investigated in this study, as 2.5 mg/kg is the maximum planned dose. Dose exploration schema will be described for each sub-study, in the appropriate sections.

For participants enrolled in the DE Phase, once RP2D is established within a sub-study, intra-participant dose escalations or de-escalation to the RP2D of both belantamab mafodotin and the sub-study partner treatment may be considered on a case-by-case basis. In the case of dose-escalation to RP2D, it will be required that the participants completed at least 2 cycles at originally assigned dose and has completed at least 1 disease assessment after the second cycle, has tolerated treatment well, and did not experience a treatment-related Grade 3 or higher toxicity.

6.6.3. Belantamab Mafodotin Dose Modification in CE Monotherapy Control Arm

The permitted dose reductions for participants in the CE Phase, in the belantamab mafodotin monotherapy control arm, are described in Table 17.

Table 17 Permitted Dose Reductions per Participant for Belantamab Mafodotin Monotherapy

Belantamab Mafodotin Dose Level	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction	4th Dose Reduction
2.5 mg/kg	1.9 mg/kg	1.4 mg/kg	1.0 mg/kg	0.75 mg/kg

6.6.4. Belantamab Mafodotin Dose Reductions or Delays

In the DE and CE Phases of the study, dose modifications may be made for individual participants, based on safety findings for that participant. After Cycle 1, participants may have their belantamab mafodotin dose reduced or delayed for toxicities. Detailed guidance for dose modifications for AEs associated with belantamab mafodotin are shown in Table 18. Dose modification guidelines for belantamab mafodotin

treatment-associated corneal events/toxicity based on the KVA Scale (Table 19) are shown in Table 20. Individual cases and any dose reductions and/or delays other than as specified must be discussed and agreed with the Medical Director.

If a dose is delayed, the participant should wait for the next scheduled dose to resume treatment. In individual cases where in the judgment of the investigator waiting a full cycle to resume treatment after delay (skipping dose) related to toxicity which has resolved would be detrimental to the participant's health, the principal investigator should contact the Medical Director to discuss an earlier restart. An earlier restart may be considered only for participants who have recovered from toxicity to at least Grade ≤1. The dosing with belantamab mafodotin cannot occur more frequently than every 21 days (+3-day window). In such cases, efficacy and safety assessments must remain every 3 weeks in line with initial efficacy and safety assessments on study, which may result in 2 separate visits (1 for dosing, 1 for disease assessments). Evaluations associated with a dose would be entered into the eCRF under the next scheduled cycle.

Dosing delays are permitted in the case of medical/surgical events or for logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, participant vacation, and/or holidays, but not for participants' decision to delay treatment). The reason for any dose delay must be documented in the participants eCRF and clinic record and discussed with the Medical Director.

The maximum dose delay without evidence of disease progression or significant toxicity associated with investigational products allowed for belantamab mafodotin is 16 weeks, unless agreed in writing by the Medical Director.

Table 18 Dose Modification Guidelines for Belantamab Mafodotin-Associated Adverse Events

Toxicity	Grade/Description of Toxicity	Recommendations
Infusion related reactions (IRRs)		• See Section 11.1.1
Serum creatinine Graded according to NCI-CTCAE criteria	Grade 2 >1.5 - 3.0 x baseline >1.5 - 3.0 x ULN	• Repeat within 48 hours if elevation cannot be explained by concomitant sepsis, TLS, other severe condition with fever or dehydration. • If confirmed: withhold belantamab mafodotin, initiate treatment and monitoring as clinically indicated, and follow for resolution. • Discuss any further treatment with belantamab mafodotin with Medical Director[1].
	Grade 3 >3.0 x baseline or Grade 4 >6.0 x ULN	• Provide appropriate medical treatment. • If drug-related, permanently discontinue treatment with belantamab mafodotin. • If due to another cause (such as sepsis, or dehydration) withhold treatment with belantamab mafodotin. Upon recovery to Grade 1, restart treatment at the same dose level.

Toxicity	Grade/Description of Toxicity	Recommendations

Spot urine (albumin/creatinine ratios)	>2000 mg/g (or 224 mg/mmol)	• Re-test (at least 7 days apart).
		• If not confirmed, continue belantamab mafodotin at current dose.
		• If confirmed on re-test and no clear evidence of disease progression:
		  • Interrupt treatment with belantamab mafodotin;
		  • Repeat testing within 4 weeks;
		  • If spot urine <2000 mg/g (224 mg/mmol), may restart belantamab mafodotin with a dose reduction;
		  • If spot urine remains >2000 mg/g (224 mg/mmol) after 4 weeks, consider permanently discontinuing belantamab mafodotin, provide treatment as clinically indicated, and follow for resolution[1].

Urine dipstick	2+	13. May continue belantamab mafodotin dosing. 14. Confirm by quantitative assessment using albumin/creatinine (spot urine from first void). • If albumin/creatinine ≥2000 mg/g, at the next cycle follow guidance above for Spot Urine.
	≥3+	• Interrupt treatment and follow-up for recovery. Implement quantification of albumin/creatinine ratio.
Thrombocytopenia (on days of dosing) Graded according to NCI-CTCAE criteria	Grade 3	• **No bleeding**: continue treatment with 1 dose level reduction. Consider reverting to previous dose once thrombocytopenia recovered to Grade 2 or less. • **With bleeding**: withhold the dose, continue treatment after recovery with 1 dose level reduction. • Consider additional supportive treatment (e.g., transfusion), as clinically indicated and per local practice.
	Grade 4	• Withhold the dose. Consider restarting with 1 dose level reduction if recovered, or transfused to, ≤Grade 3 only if there is no active bleeding at time of treatment restart. • If thrombocytopenia is considered disease-related, is not accompanied by bleeding, and recovers with transfusion to >25x10^9/L continuing treatment at 1 dose level reduction may be considered after discussion with the Medical Director.
Febrile Neutropenia Graded according to NCI-CTCAE criteria	Grades 3-4 Defined as: single temp of 38.3°C, or sustained 38°C for >1 hr AND ANC <1.0x10^9/L)	• Withhold the dose and immediately hospitalize participant with appropriate management, per local institutional guidance. • Consider additional supportive treatment per local practice (e.g., growth factors).

Toxicity	Grade/Description of Toxicity	Recommendations
		• Upon recovery, consider a dose reduction of belantamab mafodotin by 1 dose level, if neutropenia was associated with drug.
Neutropenia without Fever Graded according to NCI-CTCAE criteria	Grade ≥3 Defined as ANC <1.0x10^9/L	• If noted on Day 1 of any cycle, withhold belantamab mafodotin. • Resume belantamab mafodotin at pre-hold dose once neutropenia recovers to Grade ≤2 (ANC ≥1.0x10^9/L) on Day 1 of the subsequent cycle. • Prophylactic antibiotics, per physician discretion and local institutional guidance. Consider growth factors. • Local guidance must be followed for hematological monitoring, if more conservative than the protocol SoA specifications. • In cases of frequent recurrent neutropenia (ANC <1.0x10^9/L), consider dose reduction of belantamab mafodotin by 1 level.
Pneumonitis	Grade 2	• Withhold treatment with belantamab mafodotin. • Upon recovery, restart treatment with 1 dose level reduction. • If participant is already at the lowest dose level (1.9 mg/kg), then rechallenge with the same dose must be discussed with the Medical Director.
	Grade 3-4	• Permanently discontinue from treatment.

1. Further treatment may be allowed on a case-by-case basis after discussion with Medical Director who may consult GSK's nephrotoxicity panel.

Table 19 KVA Scale for Treatment-Associated Corneal Toxicities

Grade per KVA scale		Grade 1	Grade 2	Grade 3	Grade 4
Corneal Toxicities	***Corneal examination finding(s)***	Mild superficial keratopathy[1]	Moderate superficial keratopathy[2]	Severe superficial keratopathy[3]	Corneal epithelial defect[4]
	Change in BCVA[5]	Decline from baseline of 1 line on Snellen Visual Acuity	Decline from baseline of 2 or 3 lines (and Snellen Visual Acuity not worse than 20/200)	Decline from baseline by more than 3 lines (and Snellen Visual Acuity not worse than 20/200)	Snellen Visual Acuity worse than 20/200

*Dose modification should be based on the most severe finding. If eyes differ in severity, dose modification guideline should be applied based on the more severe eye.

1. Mild superficial keratopathy = mild superficial punctate keratopathy (documented worsening from baseline), **with or without** symptoms.
2. Moderate superficial keratopathy = any / or a combination of: moderate superficial punctate keratopathy, patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.
3. Severe superficial keratopathy = any / or a combination of: severe superficial punctate keratopathy, diffuse microcyst-like deposits involving the central cornea, sub-epithelial haze (central), or a new central stromal opacity.
4. Corneal epithelial defect such as corneal ulcers (with underlying stromal infiltration).
5. Changes in visual acuity due to treatment-associated corneal findings.
   - For participants who have BCVA worse than 20/20 in either eye at baseline, dose modification for that eye will be determined by the worsening of vision from baseline only (not by absolute BCVA at the visits).
   - If a participant has a baseline BCVA of 20/200 or worse in an eye, then belantamab mafodotin-associated changes in vision in the other eye will drive the dose modification. If a participant has baseline BCVA of 20/200 or worse in both the eyes, then the decision to delay or reduce belantamab mafodotin dose will be based on principal investigator's assessment of benefit vs risk based on corneal exam findings following a discussion with the qualified eye care specialist such as ophthalmologist/optometrist.

Table 20 Dose Modification for Belantamab Mafodotin Treatment based on the KVA scale

Grade per KVA Scale	Grade 1	Grade 2	Grade 3	Grade 4
Recommended Dosage Modifications[1]	Continue treatment at current dose.	Withhold belantamab mafodotin until improvement in **both** corneal examination findings **and** changes in BCVA to Grade 1 or better and resume at reduced dose level. If at the lowest dose, sustain the same dose level.	Withhold belantamab mafodotin until improvement in **both** corneal examination findings **and** changes in BCVA to Grade 1 or better and resume at reduced dose. If at the lowest dose, sustain the same dose level.	Consider permanent discontinuation of belantamab mafodotin. If based on benefit risk assessment, further treatment of belantamab mafodotin is being considered[2], withhold treatment until improvement in **both** corneal examination findings **and** change in BCVA to Grade 1 or better and resume at reduced dose. If at the lowest dose, sustain the same dose level.

1. Dose modification should be based on the most severe grade. If eyes differ in severity, dose modification guideline should be applied based on the more severe eye.
2. Grade 4 events require discussion with Medical Director prior to restart of belantamab mafodotin. For details on the required procedure see Section 7.1.2.

6.6.5. Management of Positive Hepatitis B Core Antibody Participants

Management by local hepatology or infectious disease services is required. If no subspecialist support is available, consultation with Medical Director is required prior to enrolment into the study for participants with positive hepatitis B core antibody.

- Participants who have developed detectable HBV-DNA levels during study treatment should be reviewed by local specialist(s) immediately (within 1 week), initiate appropriate therapy and monitoring.
- Study treatment should be withheld, and Medical Director should be contacted for any participant who develops detectable HBV-DNA levels. Agreement with Medical Director must be obtained prior to further dosing of study treatment.
- Follow liver monitoring/stopping guidelines per protocol for elevated liver function tests.

6.6.6. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participants medical condition.

Refer to the SoA for follow-up assessments of participants who are to be followed for disease progression and/or survival after they permanently discontinue from study treatment.

After the study treatment discontinuation, participants will undergo EOT assessments within 30 days from decision to discontinue and at least prior to the start of new anti-cancer treatment (. Participants who discontinued treatment for reasons other than PD will be followed up every 3 weeks until confirmed PD, until initiation of a new anti-cancer therapy or death. All participants with confirmed PD will be followed for OS and next subsequent anti-cancer therapy every 3 months until the end of study. End of study is defined in Section 4.4.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL FROM THE STUDY

7.1. Discontinuation of Study Treatment

Participants will receive study treatment according to the SoA (Section 1.2). Study drug must be permanently discontinued in the case of:

- Disease progression, as defined by IMWG criteria [Kumar, 2016], or unacceptable toxicity.
- Participant has met any of the protocol defined safety stopping criteria.
- Pregnancy.

In addition, study treatment may be permanently discontinued for any of the following reasons:

- Deviation(s) from the protocol.
- Request of the participant or proxy (withdrawal of consent by participant or proxy).
- Investigator's discretion.
- Participant is lost to follow-up.
- The study is closed or terminated.

If the participant voluntarily discontinues from treatment due to toxicity, the AE will be recorded as the primary reason for permanent discontinuation on the eCRF.

Once a participant has permanently discontinued a study treatment, the participant will not be allowed to restart study treatment.

All participants who permanently discontinue study treatment will have safety assessments at the time of discontinuation and during EOT as specified in the SoA.

Discontinuation of study treatment does not impact a participant's participation in the study. The participant should comply to the protocol schedule of assessments and data collection should continue.

If the participant does not agree to continue in-person visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the participant, contact with a relative or treating physician, or collecting information from medical records. The approach taken should be recorded in the medical records. A participant who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Participants who permanently discontinue study treatment for reasons other than disease progression will remain in the study and will be followed for PFS according to the protocol schedule described in Section 1.3 until (whichever occurs first):

- New anti-cancer therapy is initiated, or
- Disease progression according to IMWG criteria, or
- Death, or
- Withdrawal of consent, or
- Lost to follow-up, or
- End of study.

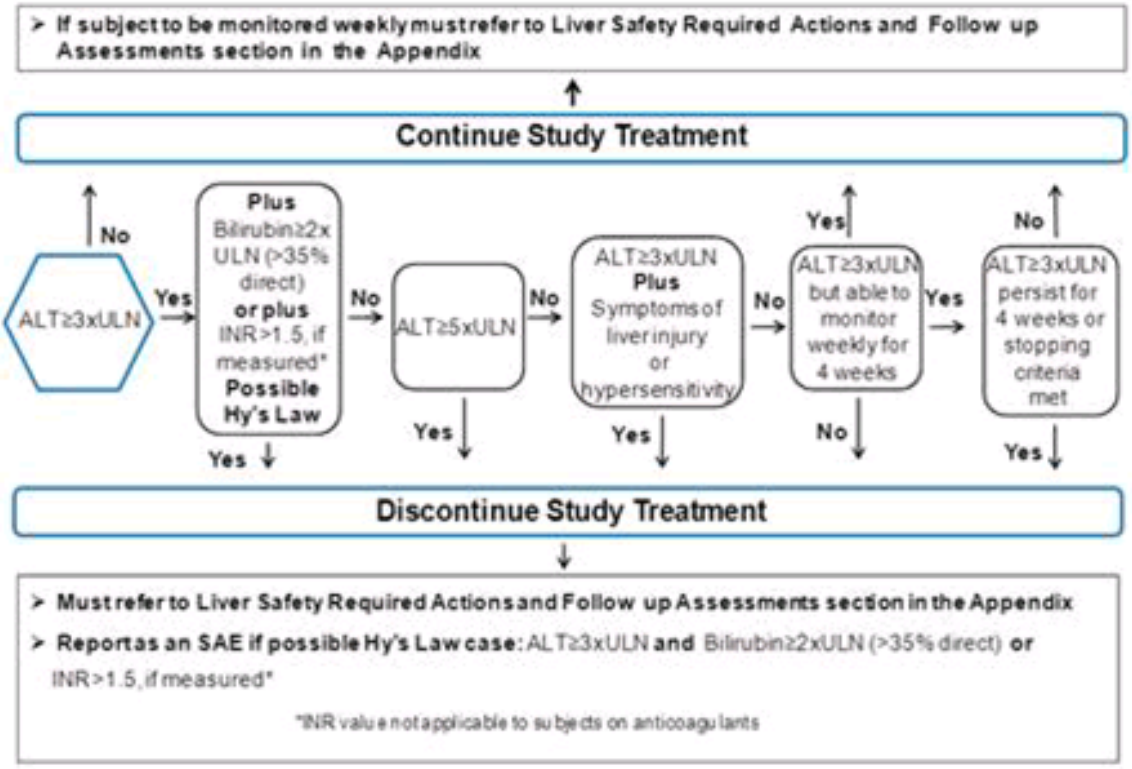
Participants with documented disease progression while on treatment, or during PFS follow-up, will be followed for OS until death, withdrawal of consent, loss to follow-up or the end of study (as described in Section 1.2), whichever occurs first.

If a participant discontinues the partner treatment but remains on belantamab mafodotin alone, the participant will not be considered to have discontinued study treatment. If for any reason a participant discontinues belantamab mafodotin, they will also need to withdraw from the partner treatment; therefore, in this situation they will discontinue study treatment.

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology. Discontinuation of study treatment for abnormal liver tests is required when the participant satisfies any of the stopping rules as shown in Figure 4.

Figure 4 Liver stopping and monitoring event algorithm



1. Refer to Appendix 9 (Table 33) for required liver safety actions and follow-up assessments).

7.1.1.1. Study Treatment Restart or Rechallenge

If participant meets liver chemistry stopping criteria do not restart/rechallenge participant with study treatment unless:

- GSK Medical Governance approval **is granted, and**
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the participant.

See also Section 12.9.1 Liver Safety Drug Restart or Rechallenge guidelines.

Refer to the SRM or Appendix 9 for full guidance on consent forms and sample collection process.

7.1.2. Corneal Event Stopping Criteria

Belantamab mafodotin dose modifications and stopping criteria for treatment-related changes in visual acuity according to the KVA scale (Table 19) are detailed in Table 20.

Participants who develop Grade 4 corneal events according to the KVA scale criteria for eye disorders must be discussed in detail between the qualified, treating eye care specialist, the Medical Director and possibly a third party ophthalmologist, in order to

determine whether the participant can be allowed to continue treatment with belantamab mafodotin, or permanently discontinue treatment. The decision will be documented in study files, together with individual assessment of risk-benefit. For details on restart guidance including potential dose reductions, see Table 20.

7.1.3. Infusion-Related Reaction Management and Stopping Criteria

Premedication for belantamab mafodotin is not required prior to infusion unless deemed medically appropriate by the investigator. Premedication should be considered in any participant who experienced an IRR at first or any subsequent infusion with belantamab mafodotin.

IRRs should be managed by guidelines provided in Section 11. A participant that experiences a Grade 4 IRR associated with belantamab mafodotin should permanently discontinue study treatment.

7.1.4. Allergic and Anaphylactic Reaction Stopping Criteria

All participants will be monitored carefully for evidence of allergic response. A participant that exhibits signs or symptoms of severe hypersensitivity or anaphylaxis will receive appropriate medical treatment and will permanently discontinue study treatment.

7.2. Participant Withdrawal from the Study

A participant may withdraw from the study treatment or the study overall at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator. The investigator may withdraw the participant from study treatment for safety, behavioral or compliance reasons. This is expected to be uncommon. The investigator may withdraw the participant from the study overall for behavioral, compliance or administrative reasons. This is expected to be uncommon.

At the time of withdrawal from the study treatment or study overall, if possible, an EOT should be conducted, as shown in the SoA. See SoA for data to be collected at the time of treatment withdrawal and follow-up and for any further evaluations that need to be completed.

If the participant is discontinuing the study overall, he/she will be permanently discontinued from all study therapies and treatments and withdrawn from the study at that time. If the participant is discontinuing study treatment only, he/she will enter follow-up until withdrawal of consent, loss to follow-up or death.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not, the participant wishes to, and/or should, continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study treatment. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites, or of the study as a whole, are handled as part of Appendix 1, Section 12.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA tables (Section 1.3; Table 3, Table 4, Table 5, Table 6) and the respective combination treatment sections (refer to the respective sub-study protocol section).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Inclusion/exclusion criteria will be assessed during screening until enrollment. A participant is considered enrolled when the investigator or designee has confirmed, through the eligibility form, that all eligibility criteria have been met. Any interval change in the participant's clinical course (e.g., laboratory values, concomitant medications, clinical condition) between enrollment and first dose of investigational product that could impact the ability of the participant to safely receive their first dose should be jointly discussed between the

investigator and medical director prior to dosing. Consider referring to Table 26, Table 27, and Table 29 for guidance as appropriate.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.
- Procedures conducted as part of the participants routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for Screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Whenever 12-lead ECG, vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and blood draws. Whenever vital signs and blood draws are scheduled for the same nominal time, vital signs should be performed prior to blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time. Detailed procedures for obtaining each assessment are provided in the SRM.

8.1. Efficacy Assessments

Clinical activity will be evaluated in all participants in the study. Standard response assessments for RRMM will be applied to clinical activity data, and include: ORR, CR, sCR, PR, VGPR, DoR, PFS, TTR – as defined in IMWG criteria [Kumar, 2016], and as data permit. In addition, the CBR (defined as a MR or better) will be evaluated and the percentage of participants achieving MRD negativity will be assessed using the NGS-based clonoSEQ assay according to IMWG criteria 2016 [Kumar, 2016], as data permit.

Every effort will be made to do confirmatory testing for response.

Clinical activity assessments and/or diagnostic criteria will be evaluated before and during treatment, per IMWG and other current practice guidelines for the management of RRMM [Bennett, 2016; Kumar, 2016; Moreau, 2017; Rajkumar, 2016]. These may include:

- Laboratory tests (serum and urine protein electrophoresis for M-protein calculation, serum and urine immunofixation, serum FLC);
- Bone marrow aspirate/biopsy for disease assessment, MRD testing;
- FISH testing;
- Imaging (e.g., CT, MRI, or PET-CT scans, and/or X-ray) for extramedullary disease and Skeletal survey.

For participants who are discontinuing IP due to PD, the confirmation of PD based on laboratory parameters must be performed from a different blood and/or urine collection, either on the same day, or preferably within 14 days of the original date of suspected disease progression, and before initiation of any new anti-myeloma therapy. This may be performed at EOT.

For participants with PD due to extramedullary disease, confirmatory scans are not required. The laboratory parameters do not need to be repeated if the extramedullary disease is the only site of progression.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA tables (Section 1.3; Table 3, Table 4, Table 5, Table 6).

8.2.1. Physical Examinations

- A complete physical examination at Screening and dosing days will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded at Screening, with weight repeated at the start of each cycle (Section 1.3; Table 3, Table 4, Table 6). Weight should be recorded up to 1 decimal to match data collected in CRF.
- Investigators should pay special attention to clinical signs related to previous serious illnesses and record any changes noted during study investigation, if any.
- During interim visits and PFS Follow-up, a brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen)

8.2.2. ECOG Performance Status

The participants performance status will be assessed using the ECOG scale (Appendix 4) as specified in the SoA (Section 1.3; Table 4, Table 6).

8.2.3. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, temperature, and pulse rate. Vital signs should be measured after resting for at least 5 minutes. Vital signs will be measured more frequently if warranted by the clinical condition of the participant. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

First Infusion: Monitoring intervals: Vital signs must be monitored at predose (within 30 minutes prior to start of infusion), at the end of infusion (+0-10 min window), and 1 hour post end of infusion (+0-10 min window). In general, participants may be discharged if considered clinically stable and all other study procedures have been completed.

Subsequent Infusions: Monitoring intervals: Vital signs must be monitored at predose (within 30 minutes prior to start of each infusion), at the end of each infusion (+0-10 min window), and 30 minutes post the end of each infusion (+0-10 min window).

Participants may be discharged after the infusion has been completed if considered clinically stable and all other study procedures have been completed.

In case of IRRs or cytokine storm, monitoring will be performed with higher frequency (per local SoC or as clinically indicated).

8.2.4. New York Heart Association Functional Scale

- Criteria for rating participants for heart failure status according to the NYHA criteria are provided in Appendix 5.

8.2.5. Electrocardiogram

A single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that measures PR, QRS, QT, and QTc intervals. All ECGs must be performed by qualified personnel at the site after the participant has at least a 5-minute rest. The QT interval must be corrected for heart rate by Fridericia's formula (QTcF).

8.2.6. Echocardiogram or MUGA Scan for LVEF

- An ECHO or MUGA scan for LVEF will be obtained at Screening to assess baseline cardiac ejection fraction and then as clinically indicated.
- The same procedure that is used at Screening should be used throughout the study.
- The evaluation of the echocardiographer should include an evaluation for LVEF.
- If an ECHO or MUGA scan for LVEF is performed on study, the results must be documented in the eCRF.

8.2.7. Ophthalmic Assessments

Study sites must establish a close collaboration with a qualified eye care specialist (ophthalmologist/optometrist, see Appendix 10) who will be responsible for assessing participants while they are on study and managing participants who develop treatment-related changes in vision associated with belantamab mafodotin. Management of participants with treatment-related changes in vision must be performed in close communication with the Medical Director and the treating, qualified eye care specialist.

Participants will be assessed by a qualified eye care specialist at Screening/baseline, and then Q3W, or as otherwise indicated in a specific sub-study protocol, regardless of dosing up to the sixth dose of belantamab mafodotin (assessment window of up to 5 days prior to dosing, but all effort should be made to schedule examinations as close to belantamab mafodotin dosing as possible).

If there are no significant KVA Grade 2 or above treatment-related ocular examination findings, change in participant symptoms or vision at the time of the sixth dose exam, participants may have their ophthalmologic exams decreased to once every 3 months.

If a participant subsequently develops vision changes or other ocular symptoms, the participant should be promptly evaluated by a qualified eye care specialist.

In case of persistent ophthalmic exam findings, newly developed ocular symptoms or vision changes, the participant will have further ophthalmologic exams at least every cycle until resolution (to baseline) or more frequently as clinically indicated by the qualified eye care specialist.

A full S*creening/baseline* ophthalmic examination for all participants must include for both eyes (OU):

1. Best corrected visual acuity.
2. Documentation of manifest refraction and the method used to obtain best corrected visual acuity.
3. Anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea.
4. Intraocular pressure measurement.
5. Dilated funduscopic exam.
6. Current glasses prescription (if applicable).

The *on treatment* and *follow-up* ophthalmic exam should be performed for both eyes (OU) as described below and in the SoA (Section 1.3):

1. Best corrected visual acuity.
2. Documentation of manifest refraction and the method used to obtain best corrected visual acuity.
3. Anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea.
4. Intraocular pressure measurement (if clinically indicated). If steroid eye drops are deemed medically necessary and prescribed, intraocular pressure must be monitored if steroid drops used for >7 days.
5. Dilated funduscopic exam (if clinically indicated).
6. Check glasses prescription as some fluctuation in prescription may be anticipated.

The end of treatment and last follow-up ophthalmic exam, if required, should match the Screening/baseline exam.

Additional examinations should be performed at the discretion of the treating eye care specialist.

8.2.8. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents (Appendix 1, Section 12.1.8). Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participants condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last cycle should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or Medical Director.
- If such values do not return to normal/baseline within a period of time, judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE (Version 5.0).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

8.3.1.1. Cohort Expansion Belantamab Mafodotin Monotherapy Control Arm

All AEs will be collected from the start of treatment until at least 70 days following discontinuation of study treatment regardless of initiation of a new anti-cancer therapy or transfer to hospice at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) will be recorded from the time a participant consents to participate in the study up to and including any follow-up.

Concomitant medications administered after the EOT should be recorded when given for SAEs/AESIs.

8.3.1.2. Combination Sub-Studies in the DE and CE Phases

The time period and frequency for collecting all (S)AEs for each sub-study will be the same as the control arm unless the properties of the combination partner dictate otherwise. These will be described in each sub-study protocol if there are different safety requirements for the sub-study.

8.3.2. Method of recording AE and SAE information

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section, except for any SAEs assessed as related to study participation as described above.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

8.3.3. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AESIs (as defined in Section 8.3, Section 8.3.10 and Section 8.3.10.2), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Concomitant medications administered after EOT should be recorded when given for SAEs/AESIs. Further information on follow-up procedures is given in Appendix 3.

8.3.5. Reporting of Potentially Life-Threatening AEs to the Medical Director

The Medical Director must be contacted by the investigator, or a designee, at the earliest possible opportunity after onset of a potentially life-threatening AE. No further doses of any of the constituent therapies of the combination should be administered to the participant. In collaboration with the SRT and the investigator, the Medical Director will assess whether the affected participant should be withdrawn from the study.

The GSK SRT will also consider whether scheduled dosing in other participants should be temporarily paused in the same dosing cohort, or the entire sub-study, pending a comprehensive review of all available data, including but not restricted to: AEs, PK profile and immunological biomarkers where applicable.

8.3.6. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- Investigator safety reports must be prepared for suspected unexpected SAEs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.7. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and 4 months following last dose of belantamab mafodotin (unless otherwise indicated in a specific sub-study protocol).
- Details of all pregnancies for female partners of male participants will be collected after the start of study treatment and 6 months following last dose of belantamab mafodotin.
- For each combination partner, the time for collection of details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and treatment will be defined within the appropriate sub-study protocol.

- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.8. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3, Section 12.3.3 and all deaths, whether or not they are considered SAEs, specific cardiovascular and death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The cardiovascular CRFs are presented as queries in response to reporting of certain cardiovascular MedDRA terms. The cardiovascular information should be recorded in the specific cardiovascular section of the CRF within 1 week of receipt of a cardiovascular event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

8.3.9. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (ie, disease progression or hospitalization due to disease progression) does not need to be reported as a SAE. Death due to disease under study is to be recorded on the Death eCRF. However, if the underlying disease (ie, progression) is greater than that which would normally be expected for the participant, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design or procedures and the disease progression, then this must be reported as a SAE.

8.3.10. Adverse Events of Special Interest

8.3.10.1. Adverse Events of Special Interest for Belantamab Mafodotin

AESIs for belantamab mafodotin are corneal events, thrombocytopenia and IRRs. Severity of all AESIs will be graded using NCI-CTCAE (Version 5.0). Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Section 11.3, Table 30. Dose modifications for belantamab mafodotin corneal events will be based on the KVA Scale (Table 19).

8.3.10.2. Adverse Events of Special Interest for Partners and Combinations

Detailed guidance for each combination partner can be found in the respective sub-study subsections (refer to the respective sub-study protocol section).

8.4. Treatment of Overdose of Belantamab Mafodotin (GSK285916)

There is no specific information on overdose of belantamab mafodotin. GSK does not recommend a specific treatment for an overdose of belantamab mafodotin.

In the event of an overdose (defined as administration of more than the protocol-specified dose) of belantamab mafodotin, the investigator should:

- Contact the Medical Director immediately.
- Closely monitor the participant for AEs, SAEs, and laboratory abnormalities until they have resolved and belantamab mafodotin concentrations are predicted to be within the anticipated range in absence of the overdose.
- Obtain an additional plasma sample for PK analysis and a blood sBCMA sample if requested by the Medical Director (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Director based on the clinical evaluation of the participant.

For each sub-study, each dose considered as overdose will be defined in the respective sub-study protocol sections.

8.5. Pharmacokinetics

8.5.1. Blood Sample Collection for Pharmacokinetics

Blood samples for PK analysis of belantamab mafodotin (ADC and optionally total antibody) and cys-mcMMAF will be collected at the time points indicated in the SoA table (Table 3, Table 4, Table 5, Table 6). For each collection of a PK sample for belantamab mafodotin, a soluble BCMA serum sample should be obtained.

Additional blood samples may be required for PK analysis of combination partners and are described in each sub-study protocol.

Each PK sample should be collected as close as possible to the planned time relative to the administration of the relevant drug during PK days (ie, belantamab mafodotin samples collected relative to belantamab mafodotin dosing). The actual date and time of each blood sample collection will be recorded. Details on PK blood sample collection including blood volumes, processing, storage, and shipping procedures are provided in the SRM and the laboratory manual.

8.5.2. Pharmacokinetic Sample Analysis

Plasma analysis will be performed under the control of GSK. Concentrations of belantamab mafodotin, optionally total antibody, and cys-mcMMAF will be determined in plasma samples using the currently approved bioanalytical methodology. Concentrations of combination partners, when applicable will be determined in plasma samples using validated bioanalytical methods. Raw data will be archived at the bioanalytical site.

Once the plasma has been analyzed for belantamab mafodotin, total antibody, and/or cys-mcMMAF, any remaining plasma may be analyzed for other compound-related metabolites or to evaluate safety or efficacy aspects related to concerns arising during or after the study and the results may be reported under a separate GSK protocol. See the respective sub-study protocol section.

All PK samples once collected can be analyzed if the sample date and time have been recorded.

8.6. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 8, for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

8.7. Immunogenicity Assessments

Serum samples for the analysis of anti-belantamab mafodotin antibodies (ADA) will be collected from all participants according to the SoA (Section 1.3). These samples will be tested by the sponsor or sponsor's designee.

Anti-belantamab mafodotin antibody samples will be tested for anti-belantamab mafodotin antibodies using a tiered-testing scheme consisting of validated Screening, confirmation, and titration assays. Briefly, all samples will be tested in the Screening assay. Samples that screen positive are considered potentially positive and will be tested for specificity in a confirmation assay. Finally, titer values will be obtained for confirmed positive samples using a titration assay. The sample results (e.g., positive or negative) and titer values (positive samples only) will be reported. Samples that test positive for anti-belantamab mafodotin antibodies may be further characterized in a validated neutralizing antibody assay to determine the neutralizing activity of the antibodies.

The detection and characterization of antibodies to belantamab mafodotin will be performed using validated assays. The anti-belantamab mafodotin antibody assay was designed to detect antibodies to belantamab mafodotin, the unconjugated monoclonal antibody and the linker-payload. Additionally, plasma samples will be collected at the same time points (see SoA - Section 1.3) as the immunogenicity samples and analyzed to determine the belantamab mafodotin plasma concentration. The belantamab mafodotin plasma concentration results will enable interpretation of the anti-belantamab mafodotin antibody data. Anti-belantamab mafodotin antibody samples will be disposed 3 months after final approved results are provided to the Clinical Study Team or its designee or upon documented study termination.

If needed, immunogenicity assessments for combination partners will be conducted as described above for belantamab mafodotin.

8.8. Biomarkers

Biomarker research is part of this study and will involve peripheral blood (whole blood, serum, and plasma), bone marrow, and tumor biopsies. sBCMA, BCMA expression in tumor cells, immune cell phenotyping, and CMMC will be investigated and the relationship of these biomarkers will be assessed relative to response to belantamab mafodotin. Any blood, serum, bone marrow, cells and tumor samples collected during this study may be used to measure novel biomarkers (and may involve RNA analysis, DNA analysis, or protein analysis) to identify factors associated with the biological and clinical responses to belantamab mafodotin. If relevant, this approach may be extended to include the identification of biomarkers associated with AEs. Unless otherwise specified, these investigations may be performed irrespective of whether a response to belantamab mafodotin is observed.

Samples will be collected at the time points indicated in the SoA (Table 3, Table 4, Table 5, Table 6, Table 7). Biomarker samples, including bone marrows and sBCMA, once collected can be analyzed as long as date and time information have been recorded.

The sample collection strategy may be adjusted on the basis of emerging data from this study or other studies involving belantamab mafodotin in order to ensure optimal evaluation of any potential biomarkers. If biomarkers potentially predictive of response or associated with AEs are identified, samples may be used for the development of validated assays and/or diagnostic tests. Additionally, novel biomarkers may also be incorporated, as data warrants. These analyses may include but are not limited to the list below.

- BCMA expression by IHC or flow cytometry and/or DNA/RNA analyses performed on bone marrow biopsies and/or aspirates or tumor tissue.
- Additionally, bone marrow and/or tumor tissue may be evaluated for any DNA/RNA changes correlating with response.
- Measurements of the serum levels of sBCMA.
- CMMC enumeration and/or omics analysis.

- Immune cell characterization and/or profiling of the bone marrow and/or peripheral blood by protein and/or DNA/RNA analyses.

For participants enrolled in a sub-study please refer to the associated sub-study protocol section for biomarker collections.

8.8.1. sBCMA Sample Analysis

The BCMA receptor undergoes gamma-secretase mediated cleavage, leading to release of the BCMA extracellular domain as sBCMA into the circulation [Laurent, 2015].

Serum samples will be collected to measure concentrations of sBCMA at the timepoints specified in the SoA using a validated assay. Details of sample preparation, storage and analysis will be provided in the SRM and the laboratory manual. Raw data will be archived at the bioanalytical site.

All sBCMA samples once collected can be analyzed if the sample date and time have been recorded.

8.8.2. Tumor Related Biomarker Analysis

While BCMA expression is present in multiple myeloma cells, there is some variability in the expression, as well as the membranous/cytosolic localization pattern. Therefore, it is important to determine if there is any association between the expression levels of BCMA on multiple myeloma cells and clinical responses. Bone marrows and/or tumor tissue will be collected at Screening and on treatment. To examine BCMA expression changes as a potential resistance mechanism, tumor tissue at disease progression (tumor biopsy or bone marrow biopsy/aspirate) is requested. These samples will be evaluated for changes in the expression of BCMA and potentially other biomarkers. Bone marrow samples will be collected during this study at the time points indicated in the SoA. BCMA expression analysis is to be performed on a bone marrow aspirate by flow cytometry. Any remaining aspirate and/or biopsy sample will be used for biomarker research, which can include immune cell characterization and/or profiling and/or DNA/RNA analyses.

8.8.3. Circulating Multiple Myeloma Cells

To evaluate a less invasive means to assess tumor cells, we will measure circulating multiple myeloma cells and, where feasible, undertake relevant omics analysis in peripheral blood samples obtained according to the SoA. Peripheral blood CMMC samples will be analyzed by a central laboratory. CMMCs have previously been associated with measures of disease burden in multiple myeloma and decreases in their levels upon treatment were associated with better outcomes, including overall survival [Fernández de Larrea, 2021; Foulk, 2018]. To assess the utility of CMMCs with respect to belantamab mafodotin, baseline levels will be compared to changes during treatment and at the end of treatment and will be investigated relative to response to belantamab mafodotin.

8.8.4. RNA Transcriptome Research

RNA expression studies may be conducted using RNA sequencing, quantitative reverse transcriptase-polymerase chain reaction and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of RNA species resulting in an RNA expression profile for bone marrow or other samples. The RNAs assayed may be those involved with the following:

1. The pathogenesis of MM.
2. The absorption, distribution, metabolism, or excretion of belantamab mafodotin.
3. The participants response to belantamab mafodotin.

In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in the response to belantamab mafodotin or the pathogenesis of MM. The RNAs that code for these proteins and/or regulatory RNAs may also be studied. This would enable the evaluation of changes in RNA expression profiles that may correlate with biological responses relating to MM and the action of belantamab mafodotin.

The samples may also be used to confirm findings by application of alternative technologies.

8.8.5. Immune Cell Phenotyping

Belantamab mafodotin multimodal mechanism of action is postulated to include induction of antibody-dependent cellular cytotoxicity and phagocytosis (ADCC/ADCP, respectively). Therefore, immune cell phenotyping will be carried out on whole blood/and or bone marrow using appropriate technologies (including, but not limited to, flow cytometry). Several different immune cell populations, including, but not limited to, the major lymphocytic cell populations (B-, T- and NK cells) and their associated phenotypic markers will be monitored. Samples will be taken prior to belantamab mafodotin treatment and during treatment as outlined in the SoA.

8.9. Health-Related Quality of Life

Four validated health-related QoL instruments will be employed in this study, to assess disease severity, disease symptoms, AEs associated with the study treatment, and general quality of life in study participants with RRMM.

All PROs will be administered to participants in different regions based on the availability of translated versions.

8.9.1. Patient Reported Outcome Version of the Common Toxicity Criteria for Adverse Events

The PRO-CTCAE is a patient reported outcome measure developed to evaluate symptomatic toxicity in patients on cancer clinical studies [Basch, 2014]. The PRO-CTCAE was designed to be used as a companion to the NCI-CTCAE, the standard lexicon for AE reporting in cancer studies. The PRO-CTCAE includes an item library of 124 items representing 78 symptomatic toxicities drawn from the CTCAE. PRO-CTCAE

provides a systematic yet flexible tool for descriptive reporting of symptomatic treatment side effects in cancer clinical studies. In the present study, a subset of items selected from the elements from the entire PRO-CTCAE (Version 1.0) item library which are most relevant for the disease and treatments will be administered, as shown in the SoA (Section 1.3; Table 4, Table 6). The PRO-CTCAE will be administered to participants in different regions based on the availability of translated versions [Basch, 2014].

8.9.2. Visual Function Safety Assessment

The impact of potential ocular change in vision on function and health-related quality of life will be assessed with the use of a visual function questionnaire: the OSDI. All participants will complete the self-administered version of the questionnaire, unless their vision prevents them from being able to complete the questionnaire on their own. Participants who are not able to complete the questionnaire on their own and require assistance should use an Interviewer-Administered format. If the Interviewer-Administered format is used, it should be read to the participants verbatim, and participant responses should be recorded directly without any interpretation. For any additional assessments conducted via telephone (either during participation in the treatment period or during follow-up), the Interviewer-Administered format should be used.

The OSDI is a 12-item questionnaire designed to assess both the frequency of dry eye symptoms and their impact on vision-related functioning [Dougherty, 2011; Schiffman, 2000]. The OSDI has demonstrated good reliability, validity, sensitivity, and specificity, and can be used as a complement to other clinical and subjective measures of dry eye disease by providing a quantifiable assessment of dry eye symptom frequency and the impact of these symptoms on vision-related functioning. The OSDI will be completed by the participants at the times shown in the SoA (Table 4, Table 6) [Dougherty, 2011; Schiffman, 2000].

8.9.3. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires

The symptoms related to multiple myeloma and its treatment, and the impact of these symptoms on daily functioning will be assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires; EORTC QLQ-C30 and IL52 (disease symptoms domain of the EORTC QLQ-MY20). The EORTC QLQ-C30 and EORTC IL 52 QLQ-MY20 will both be completed by the participants at the times shown in the SoA (Table 4, Table 6).

8.9.3.1. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module

The EORTC QLQ-C30 is a 30-item questionnaire containing both single- and multi-item measures [Aaronson, 1993]. These include 5 functional scales (Physical, Role, Cognitive, Emotional, and Social Functioning), 3 symptom scales (Fatigue, Pain, and Nausea/Vomiting), a Global Health Status/QoL scale, and 6 single items (Constipation, Diarrhea, Insomnia, Dyspnea, Appetite Loss, and Financial Difficulties). Scores for each

scale and single-item measure are averaged and transformed linearly to a score ranging from 0–100. A high score for functional scales and for Global Health Status/QoL represent better functioning ability or HRQoL, whereas a high score for symptom scales and single items represents significant symptomatology [Proskorovsky, 2014].

8.9.3.2. European Organisation for Research and Treatment of Cancer Item Library 52 (Disease Symptoms Domain of the EORTC QLQ-MY20)

The EORTC QLQ-MY20 is a supplement to the EORTC QLQ-C30 instrument used in participants with multiple myeloma [Aaronson, 1993; Cocks, 2007]. The module comprises 20 questions that address 4 myeloma-specific HRQoL domains: Disease Symptoms, Side Effects of Treatment, Future Perspective, and Body Image. Only the Disease Symptoms domain of the EORTC QLQ-MY20 will be administered, which includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity. The disease symptom domain of the EORTC QLQ-MY20 will be referred to as the EORTC IL52. As with the EORTC QLQ-C30, EORTC QLQ-MY20 domain scores are averaged and transformed linearly to a score ranging from 0-100. A high score for Disease Symptoms represents a high level of symptomatology or problems [Proskorovsky, 2014].

8.9.4. Qualitative Telephone Interviews

To further evaluate disease and treatment-related symptoms and associated impacts on function and health-related quality of life, participants will participate in qualitative interviews conducted via telephone. The interview will be conducted by a trained interviewer in the participants native language and will be audio recorded for transcription and analysis.

The qualitative interview should be conducted within approximately 21 days following the EOT. There will be a second interview which will occur by telephone approximately 6 months after EOT, which will be optional for study participants.

9. STATISTICAL CONSIDERATIONS

The study has DE Phase and CE Phase. For each sub-study, an interim analysis will be performed at the end of the DE Phase after up to 15 participants treated at each potential RP2D of the combination therapy have progressed/died, discontinued study treatment, or have had 3 efficacy assessments (1 baseline and 2 post-baseline assessments). The primary analysis in CE will be performed at 6 months after the last participant has been dosed in CE for each sub-study. The final analysis will be performed at the end of each sub-study.

9.1. Statistical Hypotheses

In the DE Phase for a sub-study, the primary endpoint is safety. One or more potential RP2Ds of the combination will be determined. No formal statistical hypothesis will be tested.

In the CE Phase, the primary objective of the study is to determine whether belantamab mafodotin plus combination partner(s) improves the response rate compared to belantamab mafodotin alone.

A combination therapy will be considered superior to belantamab mafodotin alone if the Bayesian posterior probability that ORR in the combination is greater than ORR in monotherapy is at least 90%.

9.2. Sample Size Determination

In the DE Phase, approximately up to 15 participants will be assigned to a combination dose level.

If a response rate of ≥20% and at least 2 responders in up to 15 participants are observed for the combination therapy an additional 35 participants may be randomized to each arm in the CE Phase per sub-study. However, the decision to move to the CE Phase for a treatment combination is based on the totality of the data. Eligible participants will be randomly allocated to an open sub-study CE Phase, and then randomized between combination treatment and monotherapy within that sub-study, with randomization to treatment group stratified by prior lines of therapy (3-4 vs >4). Unless a sub-study specific control group is used for the chosen CE cohort, patients randomized to monotherapy will enter the shared belantamab mafodotin monotherapy control arm, with data from this group used in CE analyses for all relevant sub-studies. Once 35 participants have been randomized to the shared belantamab mafodotin monotherapy arm, the randomization ratio for new sub-study CE Phases will change depending on the number of new CE cohorts and the timing of their entry to the study (Table 14).

9.2.1. Statistical Operating Characteristics

Operating characteristics for the interim analysis for DE for a particular dose level in a sub-study and subsequent primary analysis for CE were evaluated via simulations. These tested scenarios with different assumptions about response rate in the belantamab mafodotin monotherapy arm (p_0) and combination therapy (p_1), with the following assumptions used for all scenarios:

- 10 participants analyzed in DE.
- Sub-study continues to CE for the same dose level.
- 35 participants randomized to combination treatment and 35 to monotherapy in CE.
- Sub-study continues to primary analysis for CE regardless of the (non-binding) interim futility analysis results at CE.
- Similar efficacy expected between DE and CE in each treatment combination.

The results from these simulations are presented in Table 21.

Table 21 Operating Characteristics of the Study

True response rate	Probability of futility at end of DE (<2 responders)	Probability of meeting success criteria at primary analysis for CE[1]
p0=0.3, p1=0.3	0.15	0.059
p0=0.3, p1=0.4	0.043	0.400
p0=0.3, p1=0.5	0.01	0.809
p0=0.3, p1=0.55	0.004	0.920
p0=0.3, p1=0.6	0.003	0.972
p0=0.4, p1=0.4	0.048	0.191
p0=0.4, p1=0.5	0.011	0.557
p0=0.4, p1=0.6	0.002	0.845
p0=0.4, p1=0.65	0.001	0.917
p0=0.4, p1=0.7	0	0.965
p0=0.5, p1=0.5	0.011	0.227
p0=0.5, p1=0.6	0.002	0.513
p0=0.5, p1=0.7	0	0.772
p0=0.5, p1=0.75	0	0.885
p0=0.5, p1=0.8	0	0.949

1. Success criteria is the posterior probability (p1- p0>0)>0.9; RBest package in R3.5.1 was used for the simulation.

If the true response rate is 40% in monotherapy, the design has a 19.1% chance of falsely declaring success at primary analysis for CE if the response rate in combination therapy is also 40%. With the same response rate in monotherapy, there is a 91.7% chance of declaring success if the response rate in combination therapy is 65%. The study has a good chance of confirming a difference between the treatment arms if the response rate for the combination therapy is at least 25% more than that of the belantamab mafodotin monotherapy.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

The **ITT** is defined as all participants who were randomized to treatment and/or stratum regardless of whether the participants actually received study treatment. All efficacy endpoints in CE Phase will be evaluated based on this population.

The **Safety Population** is defined as all participants who receive at least 1 dose of any component of the combination therapy in the combination arm, or at least 1 dose of belantamab mafodotin in the monotherapy arm. Participants will be analyzed according to the treatment they actually received. All safety endpoints will be evaluated based on this population. The efficacy endpoints in DE Phase will also be evaluated based on this population.

The **PK Population** will consist of all participants in the safety population from whom at least 1 PK sample has been obtained and analyzed. This population will be the primary population for PK analyses.

The **DLT Evaluable Population** is defined as a subset of participants in DE who have received the first course of treatment containing all agents within a sub-study and followed up within Cycle 1 or withdrawn within Cycle 1 due to an AE meeting the definition of a DLT. The cycle length is determined within each specific sub-study protocol.

A participant will be considered to be DLT evaluable if:

- They complete the first course of treatment within a sub-study and are followed through Cycle 1, or
- If they have a drug-related AE meeting the definition of a DLT within Cycle 1.

Participants who discontinue study treatment before the end of Cycle 1 or who received less than 80% of (any component of) the intended dose in Cycle 1 for study drug-related toxicity or other reasons are not considered to be DLT evaluable.

Replacement: If a participant fails to receive at least 80% of the planned oral or intravenous doses within Cycle 1 for reasons other than toxicity (e.g., concurrent illness or disease progression), the participant will be replaced in the DLT evaluable population by additional participant(s) assigned to the same dose level and will not be counted as DLT evaluable.

Additional analysis populations may be defined in the SAP.

9.4. Statistical Analyses

Statistical analyses (both interim and final) will be performed by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP, and an itemized listing of the specific analyses and displays to be produced for a given analysis will be included in the relevant OPS document.

9.4.1. Participant Population Analyses

Participant disposition, treatment status, demographics, baseline characteristics (that include year of birth, sex, race, and ethnicity), medical history, prior and concomitant medications, prior anti-cancer therapies, and study treatment exposure will be summarized descriptively and listed by participant.

9.4.2. Efficacy Analyses

The primary analysis will be performed on participants from the CE Phase for a given dose level of a sub-study at 6 months after the last participant first dose in that participant cohort.

The ORR based on the responses assessed by the investigator is the primary endpoint in the CE Phase of this study. It is defined as the percentage of participants with a confirmed PR or better (ie, PR, VGPR, CR and sCR), according to the IMWG Response Criteria [Kumar, 2016]. Participants with unknown or missing response will be treated as

non-responders, ie, these participants will be included in the denominator when calculating percentages of response.

Appropriate subgroup analyses may be performed if data permit, e.g., the primary endpoint ORR may be analyzed by age (<65 years, ≥65 years), gender (female, male), ethnicity (Hispanic, non-Hispanic) and race groups (American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race), prior anti-cancer therapy, and other baseline characteristics. The estimates along with 95% exact CI will be provided. In subgroup analyses, no hypothesis testing will be performed.

The primary analysis for ORR will be based on the Bayesian approach [Neuenschwander, 2008] and will be used to compare the response rate in combination therapy with monotherapy. There is no intent to compare the response rates between combination therapies. No multiplicity adjustment will be considered.

We assume that the number of observed responses from the current n_* participants follows a binomial distribution with parameter ψ_*, ie, binomial (n_*, ψ_*). The likelihood function for the observed data y_* is $L_{y_*} \propto \psi_*^{y_*}(1-\psi_*)^{n_*-y_*}$

Because the study is intended to initiate new experimental combinations over time, the robust mixture prior [Schmidli, 2014] approach will be used in case of prior data conflict, including non-concurrent control data conflict.

The robust version of the mixture prior is:

$$\hat{P}HR(\psi_*) = (1-\omega_R)Beta(\psi_*|a_1, b_1) + \omega_R Beta(\psi_*|a_0, b_0),$$

Where a_1 and b_1 are the informative priors, a_0=0.5 and b_0=0.5 are the non-informative priors.

In the DREAMM-2 (205678) study 30 responders were observed from 97 participants with RRMM who failed prior daratumumab treatment who received 2.5mg/kg of belantamab mafodotin. So a_I=30, b_I=67 are used as the parameters for the informative prior for the belantamab mafodotin monotherapy arm.

For the combination arm, the data observed from the corresponding DE Phase cohort will be used as the informative prior, ie, a_1 and b_1 are not fixed.

ω_R is the prior probability that the participant cohort in the new study differs systematically from the historical study. The choice of initial value for ω_R is based on the degree of confidence of the similarity between the new study and the historical study. To incorporate the information from the participants from the DE phase, the initial value of 0.1 for ω_R is used for the mixture prior for the combination treatment, while 0.5 for ω_R is used for the mixture prior for monotherapy to partially incorporate the data from the previous study.

The posterior can be derived,

$$\hat{P}HR(\psi_*|y_*) = (1-\tilde{\omega}_R)Beta(\psi_*|a_1+y_*, b_1+n_*-y_*) + \tilde{\omega}_R\ Beta(\psi_*|a_0+y_*, b_0+n_*-y_*)$$

where

$$\tilde{\omega}_R \propto \frac{\omega_R f_0}{\omega_R f_0+(1-\omega_R)f_1}, f_0 = \frac{B(a_0+y_*, b_0+n_*-y_*)}{B(a_0, b_0)}, f_1 = \frac{B(a_1+y_*, b_1+n_*-y_*)}{B(a_1, b_1)}.$$

Each dose level of a combination therapy that is put forward to CE will be compared to belantamab mafodotin monotherapy separately. A particular dose level for a combination therapy will be considered superior to belantamab mafodotin monotherapy in ORR if the posterior probability of the response rate in combination being greater than the response rate in monotherapy is at least 90%.

9.4.3. Secondary Efficacy Endpoint Analyses

A frequentist approach will be used to summarize ORR as a secondary endpoint. The corresponding 95% exact CI for ORR in each treatment group will also be provided. Other secondary efficacy endpoints for the CE phase will include TTR, DoR, PFS and OS.

TTR is defined as the time between the date of randomization and the first documented evidence of response (PR or better), among participants who achieve a response (ie, confirmed PR or better).

DoR is defined as the time from first documented evidence of PR or better to PD per IMWG or death from any cause or censoring among participants who achieve confirmed PR or better. Dates for censoring will be described in the SAP.

PFS is defined as the time from randomization to the earliest date of confirmed PD per IMWG or death due to any cause or censoring. Determination of dates of PFS event and dates for censoring will be described in the SAP.

OS is defined as the time from randomization until death due to any cause or censoring. Participants who withdraw consent from the study or are lost to follow-up will be censored at the time of withdrawal or lost to follow-up. Participants who are still alive at the clinical cutoff date for the analysis will be censored at the last known alive date or last contact date. The last contact date will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

An OS analysis will be performed at the time of final ORR analysis if there is a sufficient number of death events.

For all the TTE endpoints described above, median TTE with 95% CI will be estimated employing the Kaplan-Meier method. A Kaplan-Meier survival curve will be generated. The number and percentage of participants who had the event or were censored will also be reported.

9.4.4. Exploratory Efficacy Endpoint Analyses

MRD negative rate is defined as the proportion of participants who are negative for MRD as assessed by next generation sequencing at any time point after first dose as determined by the protocol defined testing procedure. The MRD negative rate and corresponding 95% CI will be provided based on the ITT population for the CE phase. For analysis purposes, participants in the ITT population without MRD assessment will be considered as having non-negative MRD.

9.4.5. Safety Analyses

All safety analyses will be performed based on the Safety Population.

9.4.5.1. Dose-Limiting Toxicities

A mTPI [Ji, 2010] method will be used to guide dose escalation/de-escalation decisions in the DE Phase. Dose decisions and identification of a RP2D will be based on the totality of the clinical safety assessment including DLTs and adverse events that are not DLTs, laboratory, PK and PD data, as well as the guidance of mTPI and other relevant information.

9.4.5.2. mTPI Method

The mTPI design [Ji, 2010] is an extension of the toxicity probability interval method and employs a simple beta-binomial hierarchic model. The dose exploration will be guided by mTPI principles. An initial cohort of 3 participants will be recruited in DE as a starting dose level within a sub-study. If the dose is safe based on these 3 participants, up to 12 additional participants will be enrolled in this dose level. If it is not safe, 3 participants will be enrolled in a de-escalated dose or the dose level will be terminated.

Decision rules are based on calculating the UPM of 3 intervals corresponding to under-dosing, proper dosing, and overdosing in terms of toxicity. Specifically, the under-dosing interval is defined as $(0, pT - \epsilon_1)$, the overdosing interval as $(pT + \epsilon_2, 1)$, and the proper dosing interval as $(pT - \epsilon_1, pT + \epsilon_2)$, where pT is the target probability of toxicity associated with the MTD and ϵ_1 and ϵ_2 are small fractions, such as 0.05, to account for the uncertainty around the true target toxicity. A sensitivity analysis reported by Ji et al [Ji, 2010] showed that the mTPI design is robust to the specification of ε values. In addition, ϵ_1 and ϵ_2 could take different values to reflect physician preference and the nature of the disease. For advanced diseases with few treatment options, higher toxicity rates might be considered acceptable, implying a specification of $\epsilon_2 > \epsilon_1$. For less-advanced diseases, the two ϵ values could be identical or $\epsilon_1 > \epsilon_2$. The 3 dosing intervals are associated with 3 different dose-escalation decisions. The under-dosing interval corresponds to a dose escalation (E) decision, overdosing corresponds to a dose de-escalation (D) decision, and proper dosing corresponds to staying at the current dose (S). Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM implies the corresponding dose-finding decision. That decision provides the dose level to be used for future participants. If the under-dosing interval has the largest UPM, decision E, to

escalate, could be executed, and the next cohort of participants will be treated at the next higher dose level. If the overdosing interval has the largest UPM, decision D to de-escalate will be executed. Ji et al [Ji, 2010] show that the decision based on the UPM performs well compared to other dose-decision frameworks in terms of minimizing the number of participants treated at doses above the MTD while maintaining an acceptable number of participants at the MTD. Under the mTPI design, a study is terminated when either the lowest available dose is associated with a toxicity rate above the MTD or a prespecified maximum sample size is reached.

9.4.5.3. Adverse Events

All AEs whether serious or non-serious, will be reported from the start of treatment until 70 days after the last dose of study treatment regardless of initiation of a new cancer therapy or transfer to hospice, unless the participant withdraws consent for study participation. Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a study treatment will be recorded from the time a participant consents to participate in the study up to and including any follow-up. AEs will be recorded using standard medical terminology and graded according to the NCI-CTCAE (Version 5.0).

AEs will be summarized by frequency and proportion of total participants, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs, and AEs leading to discontinuation of study treatment. AEs, if listed in the NCI-CTCAE (Version 5.0) will be summarized by the maximum grade.

The incidence of deaths and the primary cause of death will be summarized.

Characteristics (e.g., number of occurrences, action taken, grade, etc.) of the following AESIs will also be summarized separately:

- Corneal events, thrombocytopenia, and IRRs.

9.4.5.4. Clinical Laboratory Evaluations

- The evaluation of clinical laboratory tests will focus on selected laboratory analytes from the hematology and blood chemistry panel.
- Descriptive statistics (mean, standard deviation, median, range) will be used to summarize laboratory values and changes from baseline in observed value at each scheduled visit or worst-case post-baseline, as appropriate.
- The worst-case toxicity grade in hematology and chemistry results during treatment will be summarized.

9.4.5.5. Other Safety Measures

Other Safety Measures: Data for vital signs, ECHOs, and ophthalmic examination findings will be summarized. For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. Further details will be provided in the SAP.

9.4.6. Analyses of Health-Related Quality of Life Data

Descriptive statistics will be used to summarize scores derived from different questionnaires and change from baseline at each scheduled visit. Additional details will be provided in the SAP.

9.4.7. Pharmacokinetic Analyses

Concentration-Time Data: Linear and semi-logarithmic individual concentration-time profiles and mean and median profiles (when appropriate) will be plotted for the belantamab mafodotin, optionally total mAb, and cys-mcMMAF and the combination partners for which PK samples are collected. Concentrations will be listed for each participant and summarized (when appropriate) by combination partner, planned time point, and dose level.

Derived PK Parameters: PK analyses will be the responsibility of Clinical Pharmacokinetics Modelling and Simulation, GSK. The belantamab mafodotin and/or combination partners concentration-time data may be combined with data from other studies and may be analyzed using a population PK approach. The planned analysis may use previously developed population PK model(s) to generate post hoc PK parameter estimates for the individual participants in this study. Based on the individual post hoc parameter values, dosing information, and sample collection times, drug concentrations at the time of sample collection will be predicted for each participant. Model evaluation will consist of comparison of model-predicted and observed concentrations. If necessary, model estimation will be performed. Results of this analysis may be provided in a separate report.

PK parameters will be listed and summarized descriptively (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV%, and 95% CI of log-transformed parameters) by combination partner, cycle, and dose level.

9.4.8. Pharmacokinetic/Pharmacodynamic Analyses

If deemed appropriate and if data permit, exposure-response relationships between belantamab mafodotin and/or combination partner exposure (e.g., dose, dose intensity, concentration, Cmax, or AUC) and clinical activity and/or toxicity (e.g., response, corneal event) may be explored using population methods, separately for each combination as appropriate. If data permit, the effects of covariates may be explored. Results of this analysis may be provided in a separate report.

9.4.9. Translational Research Analyses

The results of translational research investigations will be reported either within or separately from the main CSR. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

9.4.9.1. Analysis of Novel Biomarker Data

The results of these biomarker investigations may be reported separately from the main CSR. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize novel biomarkers.

9.4.9.2. Analysis of Genetic Data

Further details on genetic analyses are addressed in Appendix 8.

9.4.9.3. Exploratory Analyses of DNA and Protein Data

Exploratory analyses may be performed on remaining samples as part of the study by analyses of DNA, RNA and protein to understand changes in response to the treatments.

The results of exploratory investigations may be reported separately from the main CSR. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

9.4.10. Analyses of Immunogenicity Data

For each participant, the results and titers of anti-belantamab mafodotin binding antibodies will be listed for each assessment time point. The frequency and percentage of participants with positive and negative results will be summarized for each assessment time and overall for each participant by dose cohort. Detailed information will be included in the SAP.

9.5. Interim Analyses

9.5.1. Dose Exploration Phase

An IA for ORR will be performed in the DE Phase after up to 15 participants treated at the combination dose have progressed/died, discontinued study treatment, or have had 3 efficacy assessments (1 baseline and 2 post-baseline assessments). Additional interim analyses may be performed in the DE Phase for publication purposes or decision making for other sub-studies.

If the true response rate is 40%, the probability of observing less than 3 responders from 15 participants (equivalent to a 20% response rate) is ~2.7%. A minimum response rate of ≥20% and a minimum of 2 responders from up to 15 participants will be needed in order to move a particular dose level of the combination therapy to the CE Phase. However, the IA decision for transitioning each RP2D into CE Phase will be based on the totality of the clinical safety assessments, laboratory assessments, PK, biomarkers (as data permit), efficacy and any other relevant information.

9.5.2. Cohort Expansion Phase

9.5.2.1. Interim Analysis for Futility

Two interim analyses may be performed for futility evaluation for a particular dose level of a combination treatment in the CE Phase. The first interim analysis will be conducted when at least 10 CE combination treatment participants are evaluable. The second interim analysis may be performed when approximately 18 combination treatment participants are evaluable. participants are considered evaluable if they have progressed/died, discontinued study treatment, or have had 3 post-baseline efficacy assessments or at least 2 planned doses.

At each interim analysis, the observed ORR difference between the group allocated to combination treatment and control participants allocated to monotherapy will be compared. The cohort may be discontinued if the posterior probability of response rate in combination being greater than the response rate in monotherapy is less than 40%. The posterior probability will be calculated using the method described in Section 9.4.2. The final decision to continue or not will be based on the totality of available data.

At the primary analysis, a particular dose level of combination treatment will be considered superior to monotherapy if the posterior probability of response rate in combination being greater than the response rate in monotherapy is at least 90%.

The operating characteristics of the futility decision criteria are presented in Table 22.

Table 22 Operating Characteristics of the Futility Decision Criteria

True ORR	Probability of meeting futility criteria at CE IA1[1] N=10	Probability of meeting futility criteria at CE IA2[2] N=18	Probability of meeting success criteria at primary analysis for CE[3]
p0=0.3, p1=0.3	0.370	0.253	0.028
p0=0.3, p1=0.4	0.099	0.204	0.307
p0=0.3, p1=0.5	0.026	0.081	0.759
p0=0.3, p1=0.55	0.011	0.052	0.893
p0=0.3, p1=0.6	0.005	0.028	0.951
p0=0.4, p1=0.4	0.199	0.292	0.130
p0=0.4, p1=0.5	0.081	0.126	0.491
p0=0.4, p1=0.6	0.027	0.050	0.799
p0=0.4, p1=0.65	0.020	0.027	0.893
p0=0.4, p1=0.70	<0.001	0.025	0.933

P0=True ORR in the monotherapy participants; p1=True ORR in the combination therapy participants. Futility criteria at CE IA is the posterior probability (p1- p0>0) <0.40. Success criteria at the primary analysis for CE is the posterior probability (p1- p0>0) >0.9.

1. The probability of passing DE futility threshold and then stopping at CE IA1.
2. The probability of passing DE futility threshold and passing the first IA futility threshold, and then stopping at CE IA2.
3. The probability of passing DE futility threshold and passing the CE IA futility threshold at both IAs, and then meeting the success criteria at primary analysis for CE.

Additional interim analyses may also be conducted to aid decision making regarding dose identification, cohort expansion and safety monitoring, or for publication purposes.

9.5.2.2. Rolling Safety Evaluation

In the CE Phase for a given combination treatment dose level within a sub-study, rolling evaluation for Grade 4 or higher treatment-related toxicity events which would trigger sub-study stopping criteria (see Table 23) will be performed on a per 10 participants basis for those participants treated with at least 1 cycle of belantamab mafodotin plus combination partner(s).

The observed number of treatment-related Grade 4 or higher AEs will be compared against the safety stopping rule in Table 23. The combination treatment arm will be considered to have unacceptable toxicity if the number of treatment-related Grade 4 or higher AEs is significantly higher than the number of treatment-related Grade 4 or higher AEs in the belantamab mafodotin monotherapy control arm at one-sided alpha of 0.025 (determined using normal approximation without continuity correction). Enrollment may stop if the safety stopping rule is met, considering the totality of safety data.

Table 23 Safety Stopping Rules for the Cohort Expansion

Belantamab Mafodotin Monotherapy (control) arm			**Combination sub-study arm**
Number of participants enrolled	Number of participants with treatment-related Grade 4 or higher AE	Incidence rate of participants with treatment-related Grade 4 or higher AE	Stop if treatment-related Grade 4 or higher AEs larger or equal to this number (one-sided alpha<0.025)
10	1	0.1	6
10	2	0.2	7
10	3	0.3	8
20	1	0.05	6
20	2	0.1	8
20	3	0.15	9
20	4	0.2	10
20	5	0.25	12
20	6	0.3	13
30	3	0.1	10
30	6	0.2	14
30	9	0.3	17

9.5.2.3. Ongoing Exploratory Analysis

PK and pharmacodynamic or biomarker data may be analyzed on an ongoing basis independent of prespecified interim analyses using all available data to increase the understanding of the pharmacology (including PK, pharmacodynamics, and potential diagnostic, predictive or prognostic biomarkers) of belantamab mafodotin administered with combination partners.

9.6. Sample Size Sensitivity

It is expected that the statistical operating characteristics depend on assumptions around target treatment effects, entry time of different sub-studies, and the prior probability that a new study cohort differs systematically from historical studies.

This section provides additional simulation results to evaluate the operating characteristics with different assumptions about the entry time of a new sub-study, and different initial weighting for the historical data.

9.6.1. Impact of the Timing When New Sub-Study Starts

To evaluate the impact of the timing of when a new sub-study starts, it was assumed that the new sub-study would arrive at 2, 6, or 12 months after 2 previous sub-studies commence recruitment to the CE Phase. Forecast probability of meeting the success criteria for the primary analysis of the new sub-study is shown in Table 24. Based on simulations, the timing of the new sub-study's arrival has little impact on the probability of success as this impacts the number of participants in the concurrent control and non-concurrent control due to the randomization ratio change.

Table 24 Impact of the Timing When New Sub-Study Arrives On Probability of Meeting Success Criteria

	Probability of achieving success criteria		
	2m	6m	12m
Number of concurrent control[1]	30	20	18
Number of non-concurrent control[1]	10	30	35
p0=0.3, p1=0.3	0.106	0.104	0.099
p0=0.3, p1=0.4	0.386	0.373	0.389
p0=0.3, p1=0.5	0.723	0.728	0.729
p0=0.3, p1=0.55	0.841	0.850	0.849
p0=0.3, p1=0.6	0.908	0.926	0.920
p0=0.4, p1=0.4	0.124	0.117	0.113
p0=0.4, p1=0.5	0.399	0.382	0.378
p0=0.4, p1=0.6	0.719	0.719	0.706
p0=0.4, p1=0.65	0.851	0.842	0.841
p0=0.4, p1=0.7	0.926	0.923	0.918
p0=0.5, p1=0.5	0.118	0.118	0.108
p0=0.5, p1=0.6	0.387	0.380	0.369
p0=0.5, p1=0.7	0.730	0.725	0.720
p0=0.5, p1=0.75	0.860	0.850	0.850
p0=0.5, p1=0.8	0.937	0.928	0.928

Note: This table assumes that 2 sub-studies start simultaneously in the DE Phase and both sub-studies have at least 2 responders out of a total of 10 participants in IA. Then 2 sub-studies (2 combination arms and 1 monotherapy control arm) start at the same time in the CE Phase. The enrolment rate is assumed to be 15 participants/month, divided equally between these 3 arms. A third sub-study may enter at 2m, 6m or 12m from the start of the CE Phase for the previous 2 sub-studies. The third sub-study will use non-concurrent controls from both the shared monotherapy control arm in the CE Phase and a previous study, which are used as informative components of a beta mixture prior for the monotherapy with initial weights of 0.9 and 0.1. A robust mixture prior is used for ORR with monotherapy with a weight of 0.5 for the non-informative component for both the monotherapy and combination treatments. A beta (0.5, 0.5) distribution was used as the non-informative component in the robust mixture prior.

1. The changes in the number of concurrent control and non-concurrent control participants are due to the randomization ratio changes.

9.6.2. Impact of Initial Weight Given to the Historical Data

To evaluate the impact of the initial weight given to the historical data (w.c) from a previous study on the probability of meeting the success criteria for the primary analysis, different initial weights for the informative prior for the monotherapy group were tested, while the weight given to the informative prior for the experimental combination arm is fixed. Forecast probability of meeting the success criteria is summarized in Table 25. Based on the simulations, using different initial weights for the data from previous study has minimal impact on this probability.

Table 25 Impact of the Initial Weight Given to Historical Data On Probability of Meeting Success Criteria

True response rate	Probability of achieving success criteria				
	w.e=0.9, w.c=0.9	w.e=0.9, w.c=0.7	w.e=0.9, w.c=0.5	w.e=0.9, w.c=0.3	w.e=0.9, w.c=0.1
p0=0.3, p1=0.3	0.083	0.068	0.061	0.058	0.052
p0=0.3, p1=0.4	0.369	0.373	0.386	0.409	0.415
p0=0.3, p1=0.5	0.74	0.79	0.809	0.834	0.844
p0=0.3, p1=0.55	0.874	0.905	0.924	0.937	0.946
p0=0.3, p1=0.6	0.942	0.965	0.973	0.981	0.985
p0=0.4, p1=0.4	0.124	0.161	0.195	0.214	0.258
p0=0.4, p1=0.5	0.404	0.504	0.556	0.628	0.69
p0=0.4, p1=0.6	0.73	0.796	0.847	0.888	0.93
p0=0.4, p1=0.65	0.859	0.886	0.92	0.938	0.967
p0=0.4, p1=0.7	0.932	0.95	0.963	0.975	0.984
p0=0.5, p1=0.5	0.129	0.176	0.233	0.288	0.41
p0=0.5, p1=0.6	0.382	0.44	0.511	0.579	0.69
p0=0.5, p1=0.7	0.721	0.744	0.778	0.808	0.862
p0=0.5, p1=0.75	0.852	0.862	0.876	0.898	0.921
p0=0.5, p1=0.8	0.944	0.944	0.952	0.956	0.963

Note: w.c means the weight assigned to the data from previous study. w.e is the weight assigned to the experimental combination arm.

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11. GUIDELINES FOR DOSE MODIFICATION AND OTHER PARTNER COMBINATION TREATMENTS FOR ALL SUB-STUDIES

11.1. Management of Infusion-Related Reactions/Cytokine Release Syndrome

11.1.1. Infusion-Related Reactions

Infusion reactions are a well-documented AE associated with the administration of mAbs. Infusion reactions typically develop within 30 minutes to 2 hours after initiation of drug infusion, although symptoms may be delayed for up to 48 hours. The incidence of infusion reactions varies by mAb agent, and there are multiple mechanisms known to lead to IRRs including both IgE dependent anaphylactic and non-IgE dependent anaphylactoid hypersensitivities.

Infusion reactions may affect any organ system in the body. Most are mild in severity, although severe and even fatal reactions occur. As a group, infusion reactions (including both cytokine mediated and allergic) usually occur during or within a few hours of drug infusion. Occasionally, a reaction may occur 1 to 2 days after administration. The NCI-CTCAE (Version 5.0) for grading adverse reactions during chemotherapy administration has a scale for grading the severity of infusion reactions, cytokine release syndrome, as well as separate grading scales for allergic reactions and anaphylaxis. While use of these separate grading scales may be useful for classifying the nature of an infusion reaction for research purposes, they are less useful for clinical care, since it may not be obvious if the participant is having an allergic infusion reaction or a non- allergic infusion reaction.

Clinically, infusion reaction may present with flushing, itching, urticaria, and/or angioedema, repetitive cough, sudden nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and/or change in voice quality, faintness, tachycardia (or less often bradycardia), hypotension, hypertension and/or loss of consciousness, nausea, vomiting, abdominal cramping, and/or diarrhea, sense of impending doom, tunnel vision, dizziness, and/or seizure, severe back, chest, and pelvic pain.

Table 26 Toxicity Management and Dose Modification Guidance for IRRs

Grade, Assessment or Symptom	Guidance and Management
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Decrease rate to <50% of original infusion rate until recovery from symptoms. • Administer symptomatic treatment as appropriate. Continue study treatment(s). • If no additional complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. If symptoms do not resolve or recur on 50% of infusion rate, stop infusion and give treatment as appropriate. • Prophylactic pre-infusion medications should be given before all subsequent infusions[1].
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	• STOP infusion. • Monitor closely and provide medical treatment as clinically indicated. • If symptoms resolve to Grade ≤1: Restart the infusion at 50% of the original infusion rate after premedication with an H1receptor antagonist and acetaminophen. • Prophylactic pre-infusion medications should be given before all subsequent infusions[1].
Grade 3 Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	• STOP study treatment(s). Administer 1-2 mg/kg/day IV methylprednisolone and provide supportive measures per local standard of care. Discuss with sponsor/Medical Director. Continuation only allowed after recovery to Grade ≤1 and with premedication, and extension of infusion time (2-4 hours' infusion time is recommended). • Any future infusion requires premedication[1]. • Where belantamab mafodotin is deemed to have caused an IRR, the partner agent, if a mAb, cannot be administered on the same day. The mAb may be administered on the following day, provided the above conditions are met. • Where the Grade 3 IRR has been causally attributed to an mAb partner agent, any rechallenge of the mAb partner agent should be on a separate day, with the exception any immune-oncology activating checkpoint agonist, which should be permanently discontinued if it is causally attributed by the investigator to a Grade ≥3 IRR.
Grade 4 Life-threatening; pressor or ventilatory support indicated	• Permanently discontinue study treatment(s). • Provide medical treatment as clinically indicated.

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.

1. Subsequent infusions following IRRs may be administered at full/100% infusion rate or at a reduced rate per clinical judgment following administration of prophylactic pre-infusion medications as recommended for Grade 1,2 IRRs and as required for Grade 3 IRRs.

In case of severe IRR, emergency equipment should be available at each infusion center, and physician support will always be readily available during the period of drug administration.

11.1.2. Cytokine Release Syndrome

CRS, and when severe, cytokine "storm", have been identified as sequelae of the immune system activation associated with infusion reactions. It is characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia. CRS typically occurs within the first week after therapy but may also have a prolonged onset of symptoms as well.

Table 27 provides general guidance for the treatment of CRS by grade according to NCI-CTCAE (Version 5.0) grading criteria. However, the management of CRS for an individual study participant should follow local institutional guidelines including established pathways of care in an intensive care unit setting. **Study treatment should be stopped for any case of suspected CRS. Further management should be discussed with the Medical Director on a case-by-case basis.**

Table 27 Toxicity Management for Cytokine Release Syndrome (CRS)

Toxicity	Grade, Assessment or Symptom	Guidance and Management
CRS	Grade 1 (Fever ± constitutional symptoms)	• Supportive care; assess for infection; monitor fluid balance. • Symptomatic management of constitutional symptoms and organ toxicities.
	Grade 2 (Hypotension responsive to fluids; hypoxia responsive to <40% O2)	• IV fluid support. • Manage fever and constitutional symptoms as in Grade 1. • Supplemental oxygen. • Consider transfer to ICU if clinically indicated.
	Grade 3 (Hypotension managed with 1 pressor; hypoxia requiring ≥ 40% O2)	• Management guidelines for Grades 1 and 2. • If hypotension persists, start vasopressors, transfer to ICU, obtain echocardiogram, and initiate other methods of hemodynamic monitoring as clinically indicated. • Monitor organ function closely; management per local guidelines. • If hypotension persists, consider methylprednisolone 1-2 mg/kg/day. • Consider consultations with immunologist for refractory hypotension considering other anti-inflammatory agents and neurologist if signs/symptoms of encephalopathy are noted. • Anti-IL6(R) monoclonal antibodies (e.g., Tocilizumab) can be considered at the clinical discretion of the investigator.
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	• Continue management guidelines for Grades 1, 2 and 3. • Mechanical ventilation as clinically indicated. • Consider methylprednisolone 1 gm/day IV. • Continue critical care support as per local standard of care.

11.1.3. Supplemental Testing for Sub-Studies with Immuno-oncology Agents

In order to better understand the underlying etiology of these events, serum tryptase, CRP, ferritin, and a cytokine panel should be drawn during the occurrence of an infusion reaction/CRS of any grade. The serum tryptase, CRP and ferritin panels should be performed at the PI's designated local laboratory. The serum cytokine panel will be

performed at a GSK designated laboratory. These results will help us better understand (albeit retrospectively) the etiology of the AE.

Table 28 Analyte Testing in IRRs

Analyte Test	Relationship to Adverse Event
Serum tryptase[1]	IgE-related infusion reaction (Allergic/anaphylaxis) [Schwartz, 2006]
Serum CRP[1]	Elevated in CRS [Lee, 2014]
Serum ferritin[1]	Elevated in CRS [Lee, 2014]
Serum cytokine panel[2]	* Reported to be elevated in CRS [Lee, 2014]
(IFN-γ*^, TNF-α*^, IL-2*, IL-4, IL-5*, IL-6*^, IL-8*, IL-10*, IL-12p70, IL-13, and IL-17)	^consistently reported as elevated in CRS [Lee, 2014]

1. Performed by PI designated local laboratory
2. Performed by GSK designated laboratory

11.2. Immune-Related AEs for Sub-Studies with Immuno-Oncology Agents Only

irAEs are defined as events of potential immunologic etiology. Such events recently reported after treatment with other immune modulatory therapy include Grade ≥2 colitis, uveitis, hepatitis, and pneumonitis; Grade ≥3 diarrhea, endocrine disorders, and specific cutaneous toxicities; and other events that may be immune mediated, including, but not limited to, demyelinating polyneuropathy, myasthenia gravis-like syndrome, non-infectious myocarditis, and non-infectious pericarditis.

Before administration of study treatment, investigators must review a participant's AEs, concomitant medications, and clinical evaluation results (e.g., vital signs, laboratory results, ECGs, ECOG PS, physical exam findings, responses, etc.) as outlined to monitor for new or worsening irAEs and ensure continued dosing is appropriate.

Table 29 Toxicity Management Guidance for irAEs

Toxicity	Grade, Assessment or Symptom	Guidance and Management
AST / ALT elevation or increased bilirubin	Grade 2	Withhold • Administer corticosteroids (initial dose of 0.5- 1 mg/kg methylprednisolone or equivalent) followed by taper. • Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable.
	Grade 3 or 4	Permanently discontinue • Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper.
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold • Initiate insulin replacement therapy for participants with T1DM. • Administer anti-hyperglycemic in participants with hyperglycemia. • Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Colitis or Diarrhea (see Section 11.2.1 for further details)	Grade 1	Administer antidiarrheal and symptomatic treatment as appropriate • Symptoms resolve to baseline within 7 days: Provide close follow-up to evaluate for increased severity. • Symptoms ongoing >7 days: Consider following algorithm for Grade 2 events.
	Grade 2	Interrupt study treatment(s) Administer antidiarrheal and symptomatic treatment Consider corticosteroids Discuss with sponsor/Medical Director: • Symptoms resolve to Grade ≤1 or baseline within 3 days: Resume study treatment(s). • Symptoms ongoing >3 days, blood or mucus in stool, or ulceration/bleeding on endoscopy. • Permanently discontinue study treatment(s) unless resolved to Grade ≤1 with no requirement for steroids longer than 7 days. • Consider GI consultation and endoscopy to confirm or rule out colitis. • Start systemic corticosteroids (e.g., 0.5 mg/kg/day of prednisone or equivalent). • Continue steroids until improvement to Grade 1 or resolution; taper steroids as medically appropriate. • If symptoms continue or worsen to Grade 3-4, see below.

Toxicity	Grade, Assessment or Symptom	Guidance and Management
	Grade 3	Permanently discontinue study treatment(s) Assess for bowel perforation; do not administer corticosteroids if present Consult GI service, perform endoscopy with biopsy Administer 1-2 mg/kg/day IV methylprednisolone Discuss with sponsor/Medical Director: • If corticosteroid therapy does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. • Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. • If symptoms worsen during steroid taper, retaper starting at a higher dose followed by a more prolonged taper.
	Grade 4	Discontinue study treatment(s) permanently Immediately inform sponsor/Medical Director • Management as per Grade 3.
Pneumonitis (see Section 11.2.2 for further details)	Grade 1 (asymptomatic with radiographic findings only)	Discuss continued treatment with study drug(s) with sponsor/Medical Director Consider pulmonary consultation and/or bronchoscopy if clinically indicated • Perform serial imaging.
	Grade 2	Hold study drugs(s); Continue treatment when toxicity resolved to Grade ≤1. Consider pulmonary consultation with bronchoscopy and BAL Administer 1-2 mg/kg per day IV methylprednisolone, if considered IP related Discuss with sponsor/Medical Director If steroids indicated: • If toxicity resolves to Grade ≤1, taper steroids over at least 1 month. Permanently discontinue study drugs(s) if unable to reduce steroid dose to ≤10 mg prednisone or equivalent per day within 12 weeks. • Rechallenge with study drug(s) at the same dose(s) may be considered if a first event resolves to Grade ≤1 within 12 weeks of last dose. • Repeat chest imaging monthly as clinically indicated.

Toxicity	Grade, Assessment or Symptom	Guidance and Management
	Grade 3 and 4 or Recurrent Grade 2	Permanently discontinue study drug(s) Bronchoscopy with biopsy and BAL is recommended Administer 1-2 mg/kg per day IV methylprednisolone, if considered IP related Discuss with sponsor/Medical Director If steroids indicated: When symptoms resolve to Grade ≤1, taper steroids over at least 1 month. • If corticosteroid therapy does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45-60 days. • If symptoms worsen during steroid taper, retaper starting at a higher dose followed by a more prolonged taper. • Add anti-infective prophylaxis as appropriate.
Uveitis/Iritis (see Section 11.2.3 for further details)	Grade 1	Symptomatic treatment as appropriate • *Symptoms resolve to baseline ≤7 days:* Provide close follow-up to evaluate for increased severity. • *Symptoms ongoing >7 days*: Consider following algorithm for Grade 2 events.
	Grade 2	Hold study drug(s) Consultation with an eye care specialist is strongly recommended. Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics, if considered IP related Discuss with sponsor/Medical Director • Symptoms resolve to baseline ≤7 days: Resume study drug(s). • *Symptoms ongoing >7 days*: Discontinue study drug(s). • If symptoms continue or worsen to Grade 3 or Grade 4, see below.
	Grade 3	Permanently discontinue study drug(s) Administer 1-2 mg/kg per day IV methylprednisolone, if considered IP related (local administration of corticosteroids may be considered after consultation with an eye care specialist) Consultation with an eye care specialist is strongly recommended Discuss with sponsor/Medical Director • If applicable, continue steroids until improvement to Grade ≤1; taper steroids over at least 1 month.
	Grade 4	Permanently discontinue study drug(s) Immediately inform sponsor/Medical Director • Management as per Grade 3.

Toxicity	Grade, Assessment or Symptom	Guidance and Management
Endocrine events (see Section 11.2.4 for further details)	Grade 2 Signs and/or symptoms of dysfunction Endocrinopathies requiring hormone-replacement or medical intervention	Consider interruption of study treatment(s) if symptomatic. Assess endocrine function Consider pituitary imaging Administer up to 1 to 2 mg/kg/day IV methylprednisolone if clinically indicated. Initiate appropriate hormone-replacement therapy. Consider consultation with endocrinology Discuss with sponsor/Medical Director • Taper steroids as clinically indicated. • Consider resuming study treatment(s) when participant is stable (on hormone-replacement therapy if indicated), symptoms have resolved or return to baseline, and the participant is receiving ≤10 mg prednisone or equivalent per day.
	Grades 3-4 Adrenal crisis or other adverse reactions requiring hospitalization, urgent medical intervention	Consider interruption of study drug(s) Discuss with sponsor/Medical Director Consider immediate initiation of 1-2 mg/kg/day IV methylprednisolone Consult endocrinology Other management as above • Taper steroids over at least 1 month. • Consider resuming study treatment(s) when: • Participant is stable (on hormone-replacement therapy if indicated) and symptoms have resolved or return to baseline. • Participant is receiving ≤10 mg prednisone or equivalent per day.
Renal failure or acute kidney injury	Grade 1	Symptomatic treatment as appropriate • Symptoms resolve to baseline ≤7 days: Provide close follow-up to evaluate for increased severity. • Symptoms ongoing >7 days: Consider following algorithm for Grade 2 events.
	Grade 2	Interrupt study treatment(s)[a] Consultation with nephrology is strongly recommended Consider administration of oral or IV corticosteroids Discuss with sponsor/Medical Director: • Symptoms resolve to baseline within 7 days: Resume study treatment(s); • Symptoms ongoing >7 days: Permanently discontinue study treatment(s); • If symptoms continue or worsen to Grade 3-4, see below.

Toxicity	**Grade, Assessment or Symptom**	**Guidance and Management**
	Grade 3	Permanently discontinue study treatment(s) Administer 1-2 mg/kg/day IV methylprednisolone Consultation with nephrologist is strongly recommended Discuss with sponsor/Medical Director: • Symptoms improve to Grade ≤2: Continue steroids until improvement to Grade ≤1 or baseline; taper steroids over at least 1 month; • Symptoms ongoing ≥12 weeks: Permanently discontinue study treatment(s).
	Grade 4	Permanently discontinue study treatment(s) Immediately inform sponsor/Medical Director • Management as per Grade 3.
Skin toxicity (see Section 11.2.5 for further details)	Localized rash	Symptomatic management • Provide close follow-up.
	Non-localized rash (diffuse, ≤50% of skin)	Hold study drug(s) Discuss with sponsor/Medical Director Consider dermatology consultation and biopsy • Symptoms resolve to baseline ≤7 days: Resume study drug(s). • *Symptoms ongoing >7 days*: Start topical or systemic corticosteroids (e.g., 0.5-1 mg/kg/day of prednisone or equivalent), if considered IP related. • Continue steroids until improvement to Grade ≤1 or resolution; taper steroids as medically appropriate. • Resume study drug(s) if symptoms have improved to Grade ≤1 within 12 weeks of last dose and, if applicable, steroid dose is ≤10 mg prednisone or equivalent per day within 12 weeks. • If symptoms continue or worsen, see below.
	Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations	Permanently discontinue study drug(s) Administer 1-2 mg/kg/day IV methylprednisolone, if considered IP related Discuss with sponsor/Medical Director Consider dermatology consultation and biopsy • Treat per local standard of care.

11.2.1. Management of Gastrointestinal Events (Diarrhea or Colitis)

Signs/symptoms may include, but are not limited to, diarrhea, constipation, abdominal pain, cramping and/or bloating, nausea and/or vomiting, blood and/or mucus in stool with or without fever, rectal bleeding, peritoneal signs consistent with bowel perforation, and ileus Table 29 above provides guidance on dose modifications and management of these events. All participants who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral intake is not feasible, fluids and electrolytes should be substituted via IV infusion.

11.2.2. Management of Pneumonitis

Signs/symptoms may include, but are not limited to: dyspnea, dry cough, hemoptysis, fever, chest pain and/or tightness, abnormal breath sounds, and fatigue. If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered. Pneumonitis events may include the following AE terms: pneumonitis, interstitial lung disease, and acute interstitial pneumonitis.

If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

Differential diagnosis: All attempts should be made to rule out other causes such as metastatic disease, and bacterial or viral infection.

NOTE: It is important that participants with a suspected diagnosis of pneumonitis be managed as per the guidance in Table 29 until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics. If an alternative diagnosis is established, the participant does not require management as below; however, the AE must be reported regardless of etiology.

11.2.3. Management of Uveitis/Iritis

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g., glaucoma or cataracts). However, the AE must be reported regardless of etiology.

11.2.4. Management of Endocrine Events

Signs/symptoms may include, but are not limited to, fatigue, weakness, headache, mental status, and/or behavioral changes, fever, vision disturbances, cold intolerance, abdominal pain, unusual bowel habits, loss of appetite, nausea and/or vomiting, and hypotension. Endocrine events may include the following AE terms: new onset type 1 diabetes mellitus, adrenal insufficiency, hyperthyroidism, hypophysitis, hypopituitarism, hypothyroidism, thyroid disorder, and thyroiditis. Dose modification guidelines for endocrine events are provided in the Table below.

- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and/or electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes an adrenal crisis and must be considered a medical emergency.

11.2.5. Management of Skin Toxicity

Differential diagnosis: All attempts should be made to rule out other causes such as metastatic disease, infection, or allergic dermatitis.

11.3. Other Dose Modification and Management Guidelines

General dose modification and management guidelines are provided below for AEs not already described (Table 30).

Table 30 General Dose Modification and Management Guidelines for Drug-Related Adverse Events Not Otherwise Specified

Severity	Management	Follow-up
Grade 1	• Administer symptomatic treatment as appropriate • Continue study drug(s)[a]	• Provide close follow-up to evaluate for increased severity, no dose modification necessary.
Grade 2	• Administer symptomatic treatment • Investigate etiology • Consider consulting subspecialist, and/or diagnostic procedure	*Symptoms resolved in ≤7 days:* • Continue after resolution at the current dose. *Symptoms ongoing >7 days or worsening*: • Delay study drug[b], or consider 1 dose level reduction. • If recovery takes >3 weeks, consult Medical Director. • If symptoms continue or worsen to Grade 3-4, see below.
Grade 3	• Provide appropriate medical treatment • Consider consulting subspecialist	• Delay treatment till recovery to Grade 1 or less. • Consider 1 or 2 dose level reduction. • Consider consultation with Medical Director. **Exceptions**: Participants who develop Grade 3 toxicities which respond to standard treatment and resolve to ≤ Grade 1 within 48 hours may continue treatment at scheduled or reduced dose.
Grade 4	• Provide appropriate medical treatment • Consider consulting subspecialist • Discuss with sponsor/Medical Director	• Interrupt treatment. • Further treatment with belantamab mafodotin only allowed on individual basis if in the discussion with the Medical Director it is agreed that benefits outweigh the risks for a given participant.

1. Treatment-related decisions can be made based on local laboratory results if central results are not available or delayed.
2. In case a dose is delayed, the participant should wait for the next scheduled dose to resume treatment.

12. APPENDICES: SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

12.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

- The investigator will be responsible for the following:
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

12.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

12.1.3. Informed Consent Process

Note: In the text below, use of LAR is not applicable for Germany.

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or his/her legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before any study procedures were performed in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or his/her legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the optional exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for optional exploratory research. Participants who decline to participate will not provide this separate signature.

In case of unexpected pregnancy, the participant must be informed that personally identifiable information such as date of birth and/or sex of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.

If partners of male participants become pregnant during the study, consent will need to be obtained or notification given as per local regulation to the partner before collecting their personally identifiable information such as year of birth or date of birth and/or sex of their baby as part of safety follow-up.

12.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant's records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

12.1.5. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of clinical studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

12.1.6. Dissemination of Clinical Study Data

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.

GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve participant care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

12.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (Appendix 1, Section 12.1.8).

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents (Appendix 1, Section 12.1.8); that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.1.8. Source Documents

Source documents (as defined by ICH GCP E6 R1, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies) provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Monitoring Plan.

12.1.9. Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study treatment development.

In Dose Exploration (DE):

- Escalation and expansion of the starting dose cohort is not possible because mTPI criteria have not been fulfilled, leading to the closure of DE and therefore the affected sub-study.

- The minimum DE efficacy threshold of ≥20% response rate and 2 responders have not been attained for any DE cohort within a given sub-study.

In Cohort Expansion (CE):

- There is a statistically significantly higher rate of Grade 4 toxicities (for any AE) between the experimental CE arm of a specific sub-study and the belantamab mafodotin monotherapy common control arm (per EC: Safety Stopping Rules for the Cohort Expansion).

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.

12.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 31 will be performed by the local laboratory unless otherwise specified. Some tests (as indicated in the table) will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Pregnancy Testing:

- Refer to Section 5.1 Inclusion Criteria for Screening pregnancy criteria.
- A pregnancy test must be performed at Screening. If the test is completed within 72 hours prior to administration of the first dose, this assessment need not be repeated on C1D1.
- Pregnancy tests (serum or urine) should be performed predose within 72 hours prior to each cycle.
- Pregnancy test (serum or urine) must also be performed at EOT and 90 days (±7 days) after last study treatment. A follow-up pregnancy assessment by telephone (for WOCBP only) should be performed 4 months after the last dose of study treatment.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 31 Protocol-Required Safety Laboratory Assessments

Hematology			
Platelet Count	*Red blood cell (RBC) Indices*:	*Automated WBC Differential:*	
Red blood cell (RBC) Count	Mean corpuscular volume (MCV)	Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
White blood cell (WBC) Count (absolute)			
Hemoglobin			
Hematocrit			
Clinical Chemistry			
urea Nitrogen	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin
Creatinine	Chloride	Alanine aminotransferase (ALT)	Uric Acid
Glucose	Total carbon dioxide (CO_2)/ bicarbonate	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium (uncorrected)	Alkaline phosphatase	Total Protein
Magnesium	Phosphorous	Creatine kinase (CK)[1]	Lactate dehydrogenase (LDH)[1]
	Calcium corrected for albumin		
Routine Urinalysis			
Specific gravity, pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Spot urine (albumin/creatinine ratio)			
Other Screening tests			
Hepatitis B surface antigen (HbsAg)			
Hepatitis B core antibody (HbcAb)			
Hepatitis C (Hep C antibody – if second generation Hepatitis C antibody positive, a hepatitis C PCR test should be performed)			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only)			
For participants previously exposed to HIV, HIV PCR and CD4-Tcells testing must be performed locally. HIV viral load must be <400 copies/mL and CD4+ T-cell (CD4+) counts ≥350 cells/uL			
PK and ADA[2]			
GSK2857916 Pharmacokinetics (blood for PK) Anti-Drug Antibodies (ADA) to GSK2857916 Reference specific sub-study protocols for partner PK and ADA requirements.			

Other Laboratory Tests			
Estimated glomerular filtration rate (eGFR	Pregnancy test (urine or blood – according to local practice)	Immunoglobulin G (IgG), Immunoglobulin M (IgM), Immunoglobulin A (IgA)[4]	Immunoglobulin D (IgD), Immunoglobulin E (IgE)[4]
Beta-2 microglobulin	Kappa, lambda free light chain (LC), FLC ratio	HBV-DNA testing	genetic sample[6]
Immunofixation (urine and serum)	Serum Protein Electrophoresis (SPEP)	Urine Protein Electrophoresis (UPEP) 24 hour urine	
Bone Marrow Aspiration / Biopsy			
Bone marrow aspirate and core biopsy for local disease assessment BM biopsy and/or aspirate for BCMA expression & biomarker research[2] BM biopsy to confirm sCR (by IHC)[3] BM aspirate for Minimal Residual Disease testing[2] BM for FISH analysis[3,5]			
Biomarker Measurements[3]			
Soluble BCMA (sBCMA) (serum)			Whole blood RNA
	Peripheral blood for CMMC analysis		

1. Isoenzyme analysis should be performed (at the central laboratory) for LDH and/or CK if either of these enzymes is ≥3x ULN.
2. To be performed at central laboratory.
3. If not available locally it can be performed centrally.
4. IgD/IgE testing is only required for participants with IgD/IgE myeloma.
5. FISH testing to be performed locally at least for t(4;14), t(14;16), amp(1q), del(1p) and del(17p13). If participant is known to have tested positive for t(4;14) or t(14/16) on previous tests, FISH for those translocations does not need to be repeated, but results from previous tests are acceptable regardless of when those tests were performed. For amp(1q), del(1p) and del(17p13), FISH results from samples taken within 60 days prior to first dose are acceptable.
6. Informed consent for genetic research must be obtained before collecting a sample.

12.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

12.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they meet the definition of an AE or SAE.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening • The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical treatment to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.3.3. Definition of Cardiovascular Events

Cardiovascular Events (Definition:

Investigators will be required to fill out the specific cardiovascular event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL*.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. All SAEs, and non-serious AEs of special interest (as defined in Section 8.3, Section 8.3.10 and Section 8.3.10.2), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

12.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Director by telephone. • Contacts for SAE reporting can be found in the SRM.
SAE Reporting to GSK via Paper CRF
• Refer to the SRM for the method to transmit the SAE paper CRF and to whom the information should be sent. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

12.4. Appendix 4: ECOG Performance Status

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

1. [Oken, 1982]

12.5. Appendix 5: NYHA Functional Classification System

12.5.1. NYHA Functional Classification System

The **New York Heart Association (NYHA) Functional Classification: Class I, II, III or IV Heart Failure** [NYHA, 1994] provides a simple way of classifying the extent of heart failure. It places participants in 1 of 4 categories based on the level of limitation experienced during physical activity:

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

12.5.2. References

The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, Mass: Little, Brown & Co.; 1994:253-256.

12.6. Appendix 6: Modified Diet in Renal Disease

Table 32 Modified Diet in Renal Disease Formula

MDRD	eGFR = 175 × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American) GFR is expressed in mL/min/1.73 m^2, S_{Cr} is serum creatinine expressed in mg/dL, and age is expressed in years. The link below will auto-calculate the creatinine clearance: http://nephron.org/cgi-bin/MDRD_GFR/cgi

12.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

12.7.1. Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first cycle, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal.
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy.
   - Documented bilateral salpingectomy.
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

12.7.2. Contraception Guidance:

CONTRACEPTIVES[1] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[2] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.* • Implantable progestogen-only hormone contraception associated with inhibition of ovulation[3] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)[3] • Bilateral tubal occlusion • Vasectomized partner • Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
Highly Effective Methods[2] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly* • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[3] • oral • intravaginal • transdermal • injectable • Progestogen-only hormone contraception associated with inhibition of ovulation[3] • oral • injectable • Sexual abstinence • Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant

Note: Periodic abstinence (calendar, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

1. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
2. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
3. Male condoms must be used in addition to hormonal contraception If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

12.7.3. Collection of Pregnancy Information

At Screening and during study, for WOCBP pregnancy assessments should be done in clinic, for female partners of male participants pregnancy assessments can be done in clinic or by home pregnancy tests with results communicated by telephone to study staff.

At end of treatment and during the follow-up periods, monthly pregnancy assessments can be done either in clinic or by home pregnancy tests with follow-up of results communicated by telephone to study staff.

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any female partner of a male study participant who becomes pregnant while participating in this study and 6 months following last study treatment. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study treatment.

12.8. Appendix 8: Genetics

12.8.1. Use/Analysis Of DNA

- Genetic variation may impact a participant's response to study treatment, susceptibility, severity and progression of disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to belantamab mafodotin or multiple myeloma and related diseases. They may also be used to develop tests/assays including diagnostic tests related to belantamab mafodotin and multiple myeloma. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome as appropriate.
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to belantamab mafodotin or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on belantamab mafodotin (or study treatments of this class) or multiple myeloma continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

12.9. Appendix 9: Liver Safety: Required Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Phase 1/2 liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Table 33 Phase 1/2 Liver Chemistry Stopping Criteria and Required Follow-Up Assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥5xULN
ALT Increase	ALT ≥3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN **and** INR >1.5, if INR measured
Cannot Monitor	ALT ≥3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow-up Assessments following ANY Liver Stopping Event	
Actions	**Follow-Up Assessments**
• Report the event to GSK **within 24 hours.** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE**[2].** • Perform liver event follow-up assessments. • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below). • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to language within this Appendix). • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue participating in the study for any protocol specified follow-up assessments. **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hrs.** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline. • A specialist or hepatology consultation is recommended. **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24-72 hrs.** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline.	• Viral hepatitis serology[4]. • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for belantamab mafodotin PK analysis and a blood sample for sBCMA, obtained within 70 days after last belantamab mafodotin dose[6,7]. • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN. • Obtain complete blood count with differential to assess eosinophilia. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form. • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over-the-counter medications. • Record alcohol use on the liver event alcohol intake case report form. **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody.
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. Record the date/time of the PK/sBCMA blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK/sBCMA sample cannot be collected in the time period indicated above, do not obtain a PK/sBCMA sample. Instructions for sample handling and shipping are in the SRM and the laboratory manual.
7. PK sample should also be drawn for combination partner agent at the time PK sampling is done for belantamab mafodotin and within 70 days after last partner agent dose; See Sub-study 3 for exception to this PK collection timing.

Table 34 Phase 1/2 Oncology liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks.	• Notify the Medical Director **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline. • If at any time participant meets the liver chemistry stopping criteria, proceed as described above. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

12.9.1. Liver Safety Drug Restart or Rechallenge Guidelines

If participant meets liver chemistry stopping criteria do not restart/rechallenge participant with study treatment unless all the following conditions are met:

- GSK Medical Governance approval **is granted** (as described below), and

- IRB/IEC approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the participant.

If GSK Medical Governance approval to restart/rechallenge participant with study treatment is not granted, then participant must permanently discontinue study treatment and may continue in the study for protocol-specified follow-up assessments.

12.9.1.1. Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Rechallenge refers to resuming study treatment following drug-induced liver injury (DILI). Because of the risks associated with rechallenge after DILI, this should only be considered for a participant for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favorable.

Following DILI, drug rechallenge is associated with a 13% mortality across all drugs in prospective studies [Andrade, 2009]. Clinical outcomes vary by drug with nearly 50% fatality with halothane re-administered within 1 month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include the following:

- Hypersensitivity with initial liver injury (e.g., fever, rash, eosinophilia).
- Jaundice or bilirubin >2 x ULN with initial liver injury (direct bilirubin >35% of total).
- Participant currently exhibits severe liver injury defined by ALT >3 x ULN, bilirubin >2 x ULN (direct bilirubin >35% of total), or INR >1.5.
- SAE or fatality has been observed with drug rechallenge [Papay, 2009; Hunt, 2010].
- Evidence of drug-related preclinical liability (e.g., reactive metabolites; mitochondrial impairment) [Hunt, 2010].

Approval by GSK for rechallenge with study treatment can be considered under the following conditions:

- Investigator requests consideration of rechallenge with study treatment for a participant who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- IRB/IEC approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the participant must be provided with a clear description of the possible benefits and risks of study treatment administration including the possibility of recurrent, more severe liver injury or death.

- The participant must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, participant meets protocol defined liver chemistry stopping criteria, study treatment must be permanently discontinued.
- Medical Director, and the IRB/IEC as required, must be informed of the participant's outcome following study treatment rechallenge.
- GSK must be notified of any AEs as per Appendix 3.

12.9.1.2. Rechallenge Following Transient Liver Stopping Events Not Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, and acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with human leukocyte antigen (HLA) markers of liver injury.

Approval by GSK for study treatment restart can be considered under the following conditions:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3 x ULN).
- Possible study treatment-related liver injury has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study treatment has an identified genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate), the presence of the marker should be excluded. If study treatment-related liver injury cannot be excluded, the guidance on rechallenge in Appendix 9, Section 12.9.1.1 will apply.
- There is no evidence of alcoholic hepatitis.
- IRB/IEC approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the participant must be provided with a clear description of the possible benefits and risks of study treatment administration including the possibility of recurrent, more severe liver injury or death.

- The participant must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment restart, the participant meets protocol defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- Medical Director, and the IRB/IEC as required, must be informed of the participant's outcome following study treatment restart.
- GSK must be notified of any AEs, as per Appendix 3.

12.10. Appendix 10: Eye Care Specialist- Qualifications and Requirements

For examiners with a degree in optometry or ophthalmology, those involved in eye evaluations in the protocol must be able to provide comprehensive eye care to participants- ranging from routine check-ups to treatment and ongoing management of visual disease. This includes, at a minimum, the ability to perform the following activities:

Specifically, qualified eye care specialists must be able to perform:

- Comprehensive eye exams;
- Visual acuity with manual refraction tests and analysis of results;
- Slit lamp tests and analysis of results;
- Intraocular pressure examination;
- Dilated fundoscopic examination;
- Diagnosis and treatment of ocular issues and diseases such as keratopathy or glaucoma.

12.11. Appendix 11: Decentralized and Remote Assessment Approaches

These Home Healthcare and Telemedicine approaches may be implemented in the CE Phase only.

Decentralized Ophthalmologic Examinations

Where applicable country and local regulations and infrastructure allow, protocol- required eye examinations may be done at a specified alternative eye--care specialist clinic. Activities that may be done as part of decentralized eye examinations must follow the schedule provided in the SoA (Section 1.3) and include the following:

- Visual acuity by near chart visual acuity or pinhole;
- Slit lamp examination;
- Tonometry (intraocular pressure measurement);
- Ophthalmoscopy.

The participant should be informed of any potential risks associated with decentralized ophthalmologic examinations and sign a revised ICF, if required. IRBs/IECs should be informed and/or approve of this change in approach and the process documented in study files.

Remote Patient Reported Outcomes (PRO) Administration

Where applicable country and local regulations, and infrastructure allow, remote PRO administration may be permitted. Remote PRO administration is defined administration of protocol PROs by a qualified third party over the telephone. The remote PRO Administrator will use the versions of the PROs designed for verbal administration. The remote PRO Administrator will have access to the electronic PRO portal for the study and input participant responses as the interview is being conducted.

The participant should be informed of any potential risks associated with the remote PRO administration and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

12.12. Appendix 12: Third Parties and Subcontractors

Sub-Study	Third Party	Service Provided	Endpoint
All	GSK	Belantamab mafodotin ADA	Secondary
All	Aushon	Cytokines	Exploratory
All	Adaptive	MRD in bone marrow aspirate	Exploratory
All	Alliance	PK Cys-mcMMAF, soluble BCMA	Exploratory
All	Menarini	CMMCs	Exploratory
All	Mosaic	Bone Marrow aspirate for BCMA Expression and Biomarker Research	Exploratory
All	Q2	Sample receipt management and storage. Analysis of TBNK, BM Aspirate for BCMA and biomarker research, Liver Safety Follow-up, FISH	Exploratory
All	Sampled	Genetic sample storage	Exploratory
All	Syneos Health	PK ADC, PK mAb	Exploratory
All	Clario	PRO Questionnaires	Exploratory
All	Evidera	Exit Interviews	Exploratory
All	ThreeWire	Data Entry Support to Site	
All	Sychrogenics	Participant Narratives	
All	J-Review	Medical Review System	
All	TCS	Various publishing-related activities	
All	Trilogy Medical Writing and Consulting	Medical Writing support	
1	GSK	ADA OX40	Secondary
1	Alliance	PK OX40	Exploratory
2	GSK	ADA - ICOS	Secondary
2	Alliance	PK ICOS	Exploratory
4	Charles River	ADA Dostarlimab	Secondary
4	Charles River	PK - Dostarlimab	Exploratory
5	Labcorp	ADA ISA	Secondary
5	CellCarta	Bone Marrow Aspirate for BCMA and/or CD38 Expression and biomarker research	Exploratory
5	Labcorp	PK ISA	Exploratory
3, 6, 7	Alliance	PK Niro	Exploratory

12.13. Appendix 13: Abbreviations and Trademarks

ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular-mediated phagocytosis
AE	Adverse event
AESI	Adverse events of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APRIL	A proliferation-inducing ligand
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
AV	Atrioventricular
BAFF	B-cell activating factor of the tumor necrosis factor family
BAL	Bronchoalveolar lavage
BCG	Bacillus Calmette-Guérin
BCMA	B-cell maturation antigen
BCVA	Best corrected visual acuity
BM	Bone marrow
BP	Blood pressure
C	Cycle
CA	Competent Authority
CAR-T	Chimeric Antigen T-cell therapy
CBC	Complete blood count
CBR	Clinical benefit rate
CDISC	Clinical Data Interchange Standards Consortium
CE	Cohort Expansion (Phase)
cfDNA	Cell free deoxyribonucleic acid
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CL	Clearance
Cmax	Maximum plasma drug concentration
CMMC	Circulating multiple myeloma cells
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRF	Case report form
CRM	Continual Reassessment Method
CRP	C-reactive protein
CRS	Cytokine release syndrome
CRT	Calreticulin
CSR	Clinical study report

CT	Computer tomography
CTCAE	Common Toxicity Criteria for Adverse Events
cTn	Cardiac troponin
Ctrough	Trough plasma concentration
CYP	Cytochrome P450
CV%	Coefficient of variation percent
Cys-mcMMAF	Cysteine maleimidocaproyl monomethyl auristatin F
D	Day
DE	Dose Exploration (Phase)
DoR	Duration of response
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated Glomerular Filtration
EOI	End of infusion
EORTC IL52	European Organisation for Research and Treatment of Cancer Item Library 52
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires 30-item Core Module
EoS	End of Study
EOT	End of Treatment
FISH	Fluorescence in situ hybridization;
FLC	Free light chain
FSH	Follicle stimulating hormone
FTIH	First time in human
G-CSF	Granulocyte colony stimulating factor
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage colony stimulating factor
GSK	GlaxoSmithKline Research & Development Limited
GSK2857916	GSK anti-BCMA antibody drug conjugate (CA8 J6M0 Potelligent MMAF)
HBsAg	Hepatitis B surface antigen
HBc	Hepatitis B core
HbcAb	Hepatitis B core antibody
HBV	Hepatitis B
HCV	Hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HMGB1	High mobility group box 1
HPLC	High performance liquid chromatography

HRT	Hormone-replacement therapy
HRQoL	Health related quality of life
HSCT	Hematopoietic stem cell transplant
IA	Interim analysis
IB	Investigator's Brochure
ICD	Immunogenic cell death
ICF	Informed consent form
ICH	International Council on Harmonization
ICU	Intensive care unit
IDSL	Integrated Data Standards Library
IEC	Institutional ethics committee
IFN-γ	Interferon gamma
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IMWG	International Myeloma Working Group
INR	International normalized ratio
IP	Investigational product
IrAE(s)	Immune-related adverse event(s)
IRB	Institutional review board
IRC	Independent review committee
IRR	Infusion-related reaction
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS	Integrated voice response system
KVA	Keratopathy Visual Acuity
LAR	Legally authorized representative
LC	Light chain
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
Mc	Maleimidocaproyl
MCV	Mean corpuscular volume
MDRD	Modified diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
mm^3	Millimeter cube
MMAF	Monomethyl auristatin F
MoA	Mechanism of action
mPFS	Median PFS
MR	Minimal response
MRD	Minimal residual disease
MRI	Magnetic resonance Imaging
MSDS	Material safety data sheet

MTD	Maximum Tolerated Dose
mTPI	Modified toxicity probability interval
MUGA	Multiple gated acquisition
NCI-CTCAE	National Cancer Institute – Common Toxicity Criteria for Adverse Events
NGS	Next generation sequencing
NT-proBNP	N-terminal B-type natriuretic peptide
NK	Natural killer
NYHA	New York Heart Association
OATP	Organic anion transporter polypeptide
OPS	Output and Programming Specification
ORR	Overall response rate
OS	Overall survival
OSDI	Ocular Surface Disease Index
OU	Oculus uterque (both eyes)
PBMC	Peripheral blood mononuclear cells
PC	Plasma cells
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
POEMS	Polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes
Pgp	P-glycoprotein
PI	Proteasome inhibitor
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient reported outcome
PRO-CTCAE	Patient Reported Outcome version of the Common Term Criteria for Adverse Events
PT	Prothrombin time
Q3W	Every 3 week
QoL	Quality of life
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cell
RNA	Ribonucleic acid
Ro	Observed accumulation ratio
RP2D	Recommended Phase 2 dose
RRMM	Relapsed/refractory multiple myeloma
RT-qPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus-2
sBCMA	Soluble B-cell maturation antigen
sCR	Stringent complete response
SoA	Schedule of Activities

SoC	Standard of care
SOI	Start of infusion
SPEP	Serum protein electrophoresis
SRM	Study research manual
SRT	Safety Review Team
SPR	Surface plasmon resonance
t½	Half-life
T3	Triiodothyronine 3
T4	Triiodothyronine 4
TBNK	T-cell, B-cell and Natural Killer cells
TLS	Tumor lysis syndrome
Tmax	Time to maximum drug concentration
TNF-α	Tumor necrosis factor alpha
TSH	Thyroid Stimulating Hormone
TTE	Time to event
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
UPM	Unit probability mass
VGPR	Very good partial response
Vd	Volume of distribution
Vss	Volume of distribution at steady state
WBC	White blood cell
WFI	Water for injection
WOCBP	Women of childbearing potential

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MedDRA

12.14. Appendix 14: Country Specific Requirements

French-specific requirements

This appendix includes all applicable requirements of French Public Health Code / specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

1. **Concerning the « SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA»**

A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code law L.1121-8-1). (exception for a participant to a non-interventional study or to a participant to an interventional study if authorised by the Ethics Committee).

It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject:

- is either affiliated to or beneficiary of a social security category

- has got an authorisation by the Ethics Committee.

2. **Concerning the "STUDY GOVERNANCE CONSIDERATIONS"**

In section "Regulatory and Ethical Considerations, including the Informed Consent Process" of study protocol

- Concerning the **process for informing the subject** and/or his/her legally authorized representative, the following text is added:

French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the subject and/or his/her legally authorized representative written consent. It also contains a reference to the authorisation of ANSM and the approval from the French Ethics Committee.

Concerning the **process for obtaining** subject informed consent:

- When a research involving human being **is carried out on a minor / on an adult in the care of a "tutelle" guardian**, consent is given by their legal representative and, if the French Ethics Committee considers that the research in question, because of the seriousness of the restraints or the specificity of the medical acts involved, entails a serious risk of affecting their private life or the integrity of their body, consent is given by the family council if it has been instated, or by the judge of "tutelle" guardians.

- When research involving human being **is carried out on an adult in the care of a "curatelle" guardian**, consent is given by the subject assisted by his guardian. However, if the adult in the care of a "curatelle" guardian is invited to participate

in research which the French Ethics Committee considers, because of the seriousness of the restraints or the specificity of the medical acts involved, to entail a serious risk of affecting their private life or the integrity of their body, the matter is submitted to the judge of guardians who decides whether the adult is capable of giving her/his consent. In the case of incapacity, the judge will decide whether or not to authorise the research involving human being.

- When research involving human being, which complies with the conditions laid down in article L. 1121-8, is considered for **an adult incapable** of expressing her/his consent and not under a legal protection order, consent is given by a person of trust as defined in article L. 1111-6 and, failing this, by the family, or a person who maintains close and stable links with the subject. However, if the French Ethics Committee considers that the research in question, because of the seriousness of the restraints or the specificity of the medical acts involved, entails a serious risk of affecting their private life or the integrity of their body, consent is given by the judge of guardians.

Concerning the management of the Patient Informed Consent Forms, the following text is added:

French Patient Informed Consent Form is in duplicate (triplicate for minor subject).

The first page of the Patient Informed Consent Form is given to the investigator. The copy is kept by the patient or legally authorized representative.

- **NOTIFICATION TO THE HOSPITAL DIRECTOR**

In accordance with Article L1123-13 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-69).

- **INFORMATION TO THE HOSPITAL PHARMACIST**

In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the IB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

- **Ethnic Origin**

In accordance with the data privacy regulation, the ethnic origin, as any personal data, can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- **TESTING OF BIOLOGICAL SAMPLES**

In accordance with the French Public Health Code law – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

3. Concerning the " DATA MANAGEMENT " the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the data privacy regulation, each of these people aforesaid has a right of access, correction and opposition on their own data through GSK (Clinical Operations Department).

4. Concerning Data Privacy

In accordance with the applicable data privacy regulation, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with one of the methodology of reference **(MR-001)** or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with GSK in accordance with the legal provisions.

5. Investigational Product Accountability, Reconciliation, and Destruction

In specific situations where institutional practices dictate that the site disposes of and/or destroys IP prior to allowing the "monitor' to verify and document IP accountability, the following applies:

*"During the conduct of the Study, Investigational Product (IP) will be destroyed by the Institution prior to a GSK "**monitor**" conducting final investigational product accountability. Institution agrees that such destruction will comply with Institution's investigational product accountability procedures and will provide GSK with investigational product accountability logs and supporting documentation to verify adherence to 'Bonnes Pratiques Cliniques' (decision dated on the 24th of November 2006).*

12.15. Appendix 15: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 05: 21 January 2022

Overall Rationale for the Amendment:

The protocol has been amended to include 2 IAs for futility, allow enrollment of participants who are positive for Hepatitis B core Antibody, exclude participants who have an active renal condition, and reflect new dose modification guidance for belantamab mafodotin. In addition, clarifications were made in line with program level changes, administrative updates, and safety updates, which are summarized in the table below.

Changes listed in the table below are for the Master Protocol only. Changes for Protocol Amendment 5 that are related to specific sub-studies are tabulated at the beginning of each relevant sub-study protocol.

Section # and Name	Description of Change	Brief Rationale
Throughout document	Updated reference to GSK2857916/ belantamab mafodotin Investigator's Brochure	To refer to the most recent version of the IB
	Updated language to align with GSK2857916/ belantamab mafodotin Investigator's Brochure	To improve overall clarity and alignment with GSK2857916 Investigator's Brochure
	Minor editorial and document formatting revisions	To improve overall clarity and correct typographical errors
1.2 Schema	Renumbering of Tables and Footnotes	As a result of changes within the document
	Schema updated to reflect the interim analysis during the CE Phase	To align with updates made in Section 4.1.2 and Section 9.5.2.1.
1.3. Schedule of Activities (SoA)	Added additional procedures for participants who are positive for Hepatitis B core Antibody Added Table 8 for additional procedures for participants who are positive for Hepatitis B core Antibody	To align with the latest regulatory guidance
	Added multiple gated acquisition (MUGA) scan. Clarified text for the Treatment Period for belantamab mafodotin monotherapy CE phase for performing the same procedure (ECHOs or MUGA scan for	Updated in line with cardiac monitoring requirements across belantamab mafodotin program, based on emerging safety data

Section # and Name	Description of Change	Brief Rationale
	LVEF) at Screening to be throughout the study	
	Updated guidance on bone marrow/core biopsy sample collection	To clarify language
	Treatment Period for belantamab mafodotin monotherapy edited to reflect CE phase only; assessments for the DE phase are described in each sub-study specific module	To clarify language
	Updated text to reflect the serum protein electrophoresis (SPEP) to be performed at Q3W and the urine protein electrophoresis [UPEP]) to be performed to confirm objective response (PR or better) or if there is concern for disease progression, during the Treatment Period for belantamab mafodotin monotherapy CE phase Clarified the text suggesting the Serum immunofixation to be performed when SPEP or UPEP are negative; and performed to confirm objective response (PR or better).	To clarify language
	Removed plasma cfDNA sample collection	Revised to remove redundancy.
	Removed Cycle 1 24 hour, and Cycle 1 Day 4 collection timepoint for PK and Biomarker during the CE treatment period.	To reduce collection of blood samples and reduce patient burden
	Updated the schedule for bone marrow aspiration and sample collection, throughout the study Clarified the optional BM research wording	To clarify language
	Revised the ocular exam follow-up time period for participants with a treatment-related change in vision at the end of treatment visit from every 6 weeks to every 3 months	To align with program level updates
2.3.1 Summary of Risk Assessment	Update of Risk Assessment table to reflect current information on keratopathy, nephrotoxicity and pneumonitis (Pulmonary) from the GSK2857916/belantamab mafodotin program	Updated based on emerging data from GSK2857916/belatamab mafodotin program

Section # and Name	Description of Change	Brief Rationale
4.1. Overall Design	Addition of two interim analyses for futility during the CE phase Added the basis on which CE will be initiated	To allow early termination of the CE phase if the futility threshold is met Added for clarification
4.1.1. Dose Exploration Phase	Updated the language to allow decisions to escalate, stay, or de-escalate the dose guided by the mTPI algorithm	To clarify language
4.1.1.1. Dose-Limiting-Toxicity	Updated the DLT criteria for dose escalation for Non-hematologic (excluding) corneal toxicity, corneal events, and removed the non-applicable footnote of Table 12 as per the updates to this section	To clarify language
4.1.1.2. mTPI in Dose Exploration	Clarified text to reflect decision criteria in the mTPI Table for all cohorts that continue to recruit participants	To clarify language
4.1.2. Cohort Expansion Phase	Updated text to include interim analyses for futility Updated the randomization ratio and proportion of participants randomized to the monotherapy arm when there are concurrent arms (CE only) in Table 14	To clarify criteria for progression of combination to CE phase.
4.4.2. Study completion	Updated the definition of Sub study completion and End of study completion definition- '12 months for DE and 36 months for CE'	For clarification
5.1. Inclusion Criteria for All Participants	Added note to inclusion criteria 1 to clarify the language on country/site age requirements Removed cardiac laboratory assessments from Table 15 which was a part of Screening for adequate organ system function Added inclusion criteria 8 to include participants who are positive for HBcAb Added inclusion criteria 10 to allow participants who are currently receiving physiological doses of oral steroids (<10mg/day), inhaled steroids or ophthalmological steroids, in the study	To clarify language and to align with program level updates. To align with the latest regulatory guidance
5.2. Exclusion Criteria	Clarified language for exclusion criteria 11 and 12 to exclude participants who have tested positive for HBcAb and for Hepatitis C	To align with the latest regulatory guidance (in Section 5.1 Inclusion Criteria 8).

Section # and Name	Description of Change	Brief Rationale
	Added exclusion criteria 13 on presence of active renal conditions Removed repetitive text in the 'Note' from exclusion criteria 23	To align with emerging safety data.
5.3. Lifestyle Considerations	Updated text with SARS-CoV-2 vaccines	Clarified text to include the wording related to SARS-CoV-2 vaccines
6.2. Belantamab mafodotin Dose Administration	Updated text on administration belantamab mafodotin on Day 1 of each cycle. Clarified language of oral combination therapy and inclusion of details in sub-studies	To clarify language
6.5.2. Prohibited Concomitant Medications and Non-Drug Therapies	Addition of text on prohibiting use of live attenuated vaccines at least reflecting following the last dose of belantamab mafodotin Clarified the language on steroids reflecting administration prior to C1D1	To maintain program-wide consistency To clarify language
6.6.3. Belantamab Mafodotin Dose Modification in CE Monotherapy Control Arm	Addition of section on permitted dose reductions for participants in the CE phase in the belantamab mafodotin monotherapy control arm	To reflect new changes of the added new lower dose of belantamab mafodotin
6.6.4 Belantamab mafodotin Dose Reductions or Delays	Updated the dose modification strategy in Table 20 for Grade 2 and Grade 3 based on KVA scale	Updated for clarification
6.6.5. Management of Positive Hepatitis B Core Antibody Participants	Added section to clarify management of participants who are positive for HBcAb and dose modification guidelines for Hepatitis B reactivation	To align with the latest regulatory guidance
7.1.3 Left Ventricular Ejection Fraction (LVEF) Stopping Criteria	Removal of LVEF stopping criteria	Updated in line with cardiac monitoring requirements across belantamab mafodotin program, based on emerging safety data
8.2.6 Echocardiogram (ECHO) or MUGA Scan for LVEF	Addition of text to include MUGA scan at baseline to assess cardiac ejection fraction	Allow flexibility in methods of scans.
8.5.2 Pharmacokinetic Sample Analysis	Removed the antibody-drug conjugate (ADC) from the PK assessments	To clarify language

Section # and Name	Description of Change	Brief Rationale
and 9.4.7. Pharmacokinetic Analyses		
8.8. Biomarkers	Clarified language in biomarkers confirming usage samples for the development of validated assays and/or diagnostic tests if potentially predictive of response or associated with AEs are identified	To clarify language
8.8.3. Tumor Related Biomarker Analysis	Updated text to add BCMA expression analysis by IHC or flow cytometry. Addition of text confirming remaining aspirate and/or biopsy sample to be used for biomarker research	To add clarity
8.8.7. Circulating Cell Free DNA (cfDNA) Analysis	This section was removed during current amendment	Not required
8.9. Health-Related Quality of Life	Corrected typo to indicate 4 health-related quality of life (QoL) instruments will be employed in this study,	Corrected a typographical error
9.3. Populations for Analyses	Added text on DLT evaluable criteria	To clarify language
9.2.1. Statistical Operating Characteristics	Added more conditions under which operating characteristics will be summarized	Updated information
9.5.2.1. Interim Analysis for Futility	Added the text for interim analysis for futility	To clarify criteria for progression of combination to CE phase
9.5.2.2. Rolling Safety Evaluation	Reorganized the text on safety stopping rules for the cohort expansion under the heading of rolling safety evaluation	To clarify language
9.5.2.3. Ongoing Exploratory Analysis	Added text to clarify and reorganized the text on exploratory analysis of pharmacokinetic and pharmacodynamic or biomarker data	To clarify language
Appendix 2-Clinical Laboratory Tests	Removed mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) from red blood cell (RBC) Indices Removed the reticulocyte count and blood type assessment Removed conditional clinical chemistry tests- Troponin, N-terminal pro B-type	To allow greater flexibility to sites and clarify language.

Section # and Name	Description of Change	Brief Rationale
	natriuretic peptide, Triiodothyronine (T3), Thyroxine (T4) and Thyroid-stimulating-hormone (TSH) Updated text to move the anti-drug antibodies (ADA) assessments to sub studies. Updated few tests under Other laboratory tests- HBV-DNA testing, Coombs testing Updated the bone marrow aspiration methods	
Appendix 3.5 Reporting of SAE to GSK	Removed requirement for investigator or medically qualified sub-investigator to show evidence within the eCRF of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF	72 hour check box requirement is no longer in effect. The need for the investigator to document that they have reviewed the AE/SAE and provide an assessment of causality is covered in Section 12.3.4
Appendix 10. Eye-Care Specialist-Qualifications and Requirements	Aligned the text to reflect the requirements from eye-care specialist	To clarify language
Appendix 11. Decentralized and Remote Assessment Approaches	Updated heading from 'Home Healthcare and Telemedicine Approaches' to 'Decentralized and Remote Assessment Approaches'. Also updated the content to align with new heading	Updated with new changes
Appendix 12. Abbreviations and Trademarks	Updated the new abbreviations used in the document.	To reflect new changes
Appendix 13: Protocol Amendment History	Addition of summary of changes from amendment 04 in the appendix as per the template requirement	Template alignment

Amendment 04: 14 December 2020

Overall Rationale for the Amendment:

The protocol has been amended to introduce a new sub-study (Sub-study 5), revise the design and dose evaluation of Sub-study 3, and to convert the protocol into a modular format with separate sub-study modules.

In addition, changes were made in line with comments from regulators, program level changes and safety updates, which include the following:

- Biomarker assay added for plasma cfDNA assessment
- Guidance on avoidance of blood product transfusion on dosing days
- Added Tables on Ocular KVA scale and revised Dose Modification guidance for Ocular events based on the KVA scale
- Added instruction to check glasses prescription during follow-up ophthalmic exams
- Added Appendix outlining acceptable use of Home Health/Telemedicine approaches in circumstances where patient visits may not be performed onsite (ie, due to local COVID-19 restrictions)

Changes listed in the table below are for the Master protocol only. Changes for Protocol Amendment 4 that are related to specific sub-studies are tabulated at the beginning of each relevant sub-study module.

Section # and Name	Description of Change	Brief Rationale
Revised Study Design		
Section 1.2 Schema	Replaced study design diagram	Minor revisions to update
Introduction Changes		
Section 2.2.4.1 Pharmacokinetics and Pharmacodynamics in Humans	Edited Background information of belantamab mafodotin PK data from Study 205678	Updated data
Study Population		
Section 5.2 Exclusion Criteria	Revised exclusion criteria for plasma cell leukemia to also include past diagnosis	To clarify exclusion criteria for participants with plasma cell leukemia
Safety Changes		
Section 4.1.1.1 Dose-Limiting Toxicity	Updated Table 11 footnote to state KVA scale to be used to capture corneal toxicity and changes in visual acuity	For assessment of ocular events utilizing program KVA Scale based on feedback from regulatory agencies
Section 6.5.1 Permitted Concomitant Medications	Added guidance to avoid administration of blood product transfusions on dosing days	To avoid interference with belantamab mafodotin administration and assessment/determination of relatedness of reaction(s) due to blood product or study drug administration
Section 6.6.3 Belantamab Mafodotin dose reductions and delays	Added Table 17 for the new ocular KVA scale for grading of treatment-related corneal events	For assessment of ocular events utilizing program KVA Scale based on feedback from regulatory agencies
Section 6.6.3 Belantamab Mafodotin dose reductions and delays	Added Table 18 dose modifications, in alignment with the guidelines of the new ocular KVA scale	To provide guidance on dose modification for ocular events utilizing KVA scale per program
Section 7.1.3 QTc interval stopping criteria	Removed entire section	Clarified Safety Assessments based on prior edits (Protocol Amendment 03)
Section 7.1.4	Updated reference to the KVA Scale for corneal event assessments	For assessment of ocular events utilizing program KVA Scale based

Section # and Name	Description of Change	Brief Rationale
		on feedback from regulatory agencies
Section 8.2.5 Electrocardiogram (ECG)	Clarified language as a single ECG is only to be collected at Screening	Clarified based on prior edits (Protocol Amendment 03)
Section 8.2.7 Ophthalmic assessments	Added instruction to check glasses prescription	To accommodate for fluctuations in prescriptions
	Clarified language on significant ophthalmic findings (Grade 2 or above) and definition of resolution (to baseline instead of Grade 1)	To align with GSK belantamab mafodotin program language
Changes in Assessments and Schedules of Activities (SoAs)		
Section 1.3 SoA tables	Added language to contact the Medical Director prior to dosing in case C1D1 Hem/Chem results are outside the eligibility requirements at Screening	To clarify medical review and approval requirement for C1D1 dosing
	Clarified language on definition of resolution of ophthalmic findings (to baseline instead of Grade 1)	To align with GSK belantamab mafodotin program language
	Added plasma-cfDNA assessment	To update and clarify this assessment
	Clarified footnote on Single ECG at Screening (Table 3)	Clarified based on prior edits (Protocol Amendment 03)
	Addition of Table 7 to summarize bone marrow sampling and assessments	To summarize and provide detail on these procedures in 1 location
Section 12.11 Appendix 11	Added Appendix for Home Health/Telemedicine approaches	To provide alternative assessments in circumstances where patient visits may not be performed onsite (ie, due to local COVID-19 restrictions)
Protocol Clarification and Alignment		
Section 4.1.2 Cohort Expansion Phase	Text Clarification for prior to be used (DREAMM-2 data instead of FTIH data)	Based on available data from the pivotal DREAMM-2 study
Section 8.8 Biomarkers	Added clarifying language for analysis of biomarker samples if date and time have been recorded	To clarify time/date requirements for sample analysis
Administrative Changes		
Sub-study sections	Transferred to separate modules	Conversion to modular format
Editorial/Document Formatting Changes		
Throughout document	Minor editorial and document formatting revisions	Minor revisions without change to content, therefore have not been specifically delineated

Amendment 3: 08 July 2020

Overall Rationale for the Amendment:

The protocol has been amended to introduce a new sub-study into Section 14 of the protocol. In addition, changes were made in line with comments from regulators, program level changes and safety updates, which include the following:

- Introduction of Sub-study 4- belantamab mafodotin and partner agent combination (Section 14)
- Incorporation of updated human experience, safety information and PK/PD summary for belantamab mafodotin (Sections 2.2.4 and 2.2.4.1)
- Incorporation of updated PK/PD and safety information for partner agents in sub-studies 1 and 2 (Section 11 and Section 12).
- Removal of post-baseline ECG assessments
- Modifications to the Dose Escalation Plan (DEP)
- Revised guidance added for belantamab mafodotin overdose
- Revisions to statistical projections and analyses due to addition of sub-study 4
- Replaced asset number or abbreviations with generic name belantamab mafodotin
- Included reference for data from DREAMM-2 study [Lonial, 2020] to support 2.5 mg/kg starting dose and removal of references to 3.4 mg/kg dose
- Guidance on dose modifications modified to include/change management of IRRs, urine dipstick results, thrombocytopenia, neutropenia without fever, pneumonitis
- Modified text on Risk Assessment for thrombocytopenia, potential cardiotoxicity, immunosuppression
- Minor editorial and document formatting revisions

Changes listed in the table below are for the Master protocol only. Changes for Protocol Amendment 3 that are related to specific sub-studies are tabulated at the beginning of each relevant sub-study section (Section 11 through Section 15).

Section # and Name	Description of Change	Brief Rationale
Revised Study Design		
Section 1.1	Modified language regarding belantamab mafodotin monotherapy dose decision	See reference for DREAMM-2 study data [Lonial, 2020] for belantamab mafodotin monotherapy recommended dose
Section 1.1	Removed references to 3.4 mg/kg dose	See reference for DREAMM-2 study data [Lonial, 2020] as above
Section 1.3	Bone Marrow sample for BCMA expression-added biopsy in addition to aspirate collection for biomarker research. Replaced aspirate clot by aspirate.	Change in sample type due to observed assay failure secondary to hemodilution in bone marrow aspirate clots. BCMA IHC is validated in bone marrow biopsy samples.
Section 1.3	Added additional timepoints for cytokines, whole blood RNA, PBMCs and CMMC	To ensure consistency across sub-studies and to provide a more comprehensive longitudinal analysis of these samples.
Section 2.3.1	Risk assessment language clarified for Impaired Female Fertility-ovarian findings in rat studies	To ensure consistency in protocol language across belantamab mafodotin program

Section # and Name	Description of Change	Brief Rationale
Section 2.2.4	Updated content for human experience with belantamab mafodotin, including current safety information and selection of 2.5 mg/kg belantamab mafodotin monotherapy recommended dose.	References added for DREAMM-1 Study data [Trudel, 2019] and DREAMM-2 Study data; Lonial, 2020]; Current human experience and safety information as per belantamab mafodotin Investigator's Brochure, v8, 2020.
Section 2.2.4.1	Updated PK/PD Summary	Current PK/PD summary information for belantamab mafodotin.
Section 3	Clarification to description of Biomarkers-Exploratory Objectives	Details added to align with content in Section 8.8; no changes to objectives, assays or schedule
Section 4.1	Modified text on the effect of new sub-studies on the randomization ratio	Maintain statistical analyses
Section 4.1.1	Reference to Dose Escalation Plan added Revised description of CE dose escalation decisions	Define membership, roles, and process for dose escalation decisions
Section 5.1	1) Revised Inclusion Criteria for IC#5 ECOG scores; 2) IC#7 Update Adequate Organ System parameters; 3) Clarification to IC#10- Informed consent signature by participant or legally authorized representative (LAR)	1) Clarify Grade 2 ECOG not exclusionary if due to skeletal complications/pain due to MM; 2) Revised to match program criteria; 3) To align with text outlined under Informed Consent Process, Section 17.1.3.
Section 5.2	Removed QTcF $\geq$480 msec from exclusion criteria and move symptomatic pericarditis as evidence of cardiovascular risk to exclusion criteria for substudies 1 and 2 exclusion	Refine study population criteria
Section 5.3	Clarification on timing and use of contact lenses post-treatment	Per belantamab mafodotin program level ocular management guidance
Section 6.2	Text added to specify that belantamab mafodotin is administered first for combination sub-studies	Clarify sequence of drug administrations
Safety Changes		
Section 1.3, Section 8.3.1	AEs/SAEs will be collected until at least 70 days post EOT	As per belantamab mafodotin program safety language
Section 1.3, Section 5.1, Section 8.3.7	Revised instructions for EoT/post-treatment pregnancy testing	As per belantamab mafodotin program safety language
Section 2.3.1	Modified text on Risk Assessment for thrombocytopenia, potential cardiotoxicity, immunosuppression	As per belantamab mafodotin program safety language
Section 6.6.3, Section 8.3.9.1	Dose modifications revised to include/change IRRs, urine dipstick results, thrombocytopenia, neutropenia without fever, pneumonitis	Clarification of urine dipstick language and remainder per belantamab mafodotin program safety language
Section 7.1.3	Text on QTc stopping criteria modified	As per belantamab mafodotin program safety language
Section 7.1.5	Revised text on stopping criteria for ocular examination findings	As per belantamab mafodotin program safety language
Section 8.2.5	Revised text on ECG assessments to reflect ECG at screening only	Consistency with change to ECG assessment at screening only
Section 8.4	Revised wording on treatment of belantamab mafodotin overdose	To provide clarification of monitoring and actions to be taken

Section # and Name	Description of Change	Brief Rationale
Section 16.3	Addition of dose modification and management table	Update based on current safety assessment
Section 17.9	Update in follow-up assessments	Revised to match current safety assessment
Changes in Assessments and Schedules of Activities (SoAs)		
Section 1.3	Revised assessments and descriptions, including: • Urinalysis assessment and description • Removal of post-baseline ECG assessments; screening and post-baseline thyroid function tests, NT-proBNP and troponin • Description of MRI, CT, PET/CT scans for disease assessment in Germany • Removal of Qualitative phone interview during treatment; optional after EoT • Serum Immunofixation and serum FLC assay • Removal of post EOT ADA sampling	Provide clarifications and more specific guidance
Section 8.8.7	Added circulating cell free DNA analysis	Specify sampling and assessment
Section 8.9.3.2	Revisions to QoL assessments to include IL52 (symptom assessment) portion of EORTC QLQ-My20 and revise timepoints	Clarify assessments and timing
Section 8.9.4	Revisions to qualitative phone interviews	Changes to timepoints and implementation
Protocol Clarification and Alignment		
Section 1.3, Section 8.2.7	Replace ophthalmologist and optometrist with eye-care specialist term and define same	Simplify and define provider terminology
Section 4.1.2	Add text for stratification based on prior lines of therapy (3-4 vs. >4)	Consistency in document
Section 6.6.3, Table 15	Clarified language to include Febrile Neutropenia and Neutropenia without Fever terms	Clarification
Section 8.2.7	Revised wording on slit lamp examinations	To align with belantamab mafodotin program guidance
Section 1.3, 3, Section 8.9.3	Update of QoL assessment name EORTC IL52 QLQ-My20	
Section 9.2.1	Updated probability rates futility/success	Revisions for consistency with protocol changes
Section 9.3	Modified definition for ITT population; update definition of DLT Evaluable population	Include stratification factor and clarification
Section 9.4.2	Revised projections of responders	Based on DREAMM2 study data [Lonial, 2020]
Section 9.6	Updated futility/success probabilities	Revised for addition of new sub-study and DREAMM2 study data [Lonial, 2020]
Throughout	Asset numbers/abbreviations replaced with generic names except for laboratory sampling	Consistency throughout document
Administrative Changes		
Throughout	The term 'Medical Monitor' has been replaced with 'Medical Director'	To better represent the medical oversight for the study
Section 17.10	Added appendix to define qualified eye-care specialist requirements	Clarify needs for ophthalmic monitoring and assessment

Section # and Name	Description of Change	Brief Rationale
Editorial/Document Formatting Changes		
Throughout document	Minor editorial and document formatting revisions	Minor revisions without change to content, therefore have not been specifically delineated

Amendment 2: 16 December 2019

Overall Rationale for the Amendment:

The protocol was amended to introduce a new sub-study into Section 13 of the protocol. In addition, changes were made in line with comments from regulators, program level changes and safety updates, which include the following:

- Updated program level wording for belantamab mafodotin mode of action
- Data updates in line with new publications
- Restricted eligibility of participants treated with prior BCMA-targeted agents to the Dose Exploration (DE) phase only
- Ophthalmology wording updated
- Updated pregnancy and contraceptive wording
- Updated timing of SAE assessments
- Toxicity Management and Dose Modification Guidance for infusion-related reactions (IRRs) wording updated
- Clarifications to the SoA.
- Clarification of efficacy evaluations
- Clarity of wording around when a sub-study can be closed, and end of study and study withdrawal defined
- Wording clarified around the starting dose of belantamab mafodotin
- New data regarding the role of B-Cell Maturation Antigen in Multiple Myeloma.
- Interim analysis timing clarified
- Live, live/attenuated vaccine timing clarified
- Infusion timing added for belantamab mafodotin
- Clarification of wording around belantamab mafodotin dose modification
- Clarification around who the SRT comprises of and meeting timings
- Definition of source data added
- Minor editorial and document formatting revisions

Changes listed in the table below are for the Master protocol only. Changes for Protocol Amendment 2 that are related to specific sub-studies are tabulated at the beginning of each relevant sub-study section (Section 11 to Section 15).

Section # and Name	Description of Change	Brief Rationale
Revised Study Design		
Section 1.1, Section 2.1, Section 2.2.4, Section 2.3.2	PFS data updated, duration of response date added. Clinical experience with belantamab mafodotin data updated.	Data updated in line with new publications.
Section 4.1 Figure 3	Removed 'each at least 24 hours apart' for participants 4 to 10 in Figure 3.	In line with other protocols in the program.
Section 5.2 Exclusion Criteria	Restricted eligibility of participants treated with prior BCMA-targeted agents to the DE phase only.	Updated in line with protocol review board recommendations.
Safety Changes		
Section 1.3, Section 7.1.5, Section 8.2.7	Ophthalmology wording updated throughout the protocol. Changes in the frequency of assessments. The GSK scale removed, steroid eye drops not mandatory and corneal images no longer required. Updated stopping criteria based on ocular examination findings.	Changes made based on results and experience from ongoing belantamab mafodotin clinical trials.
Section 2.3.1 Table 7 Risk Assessment for belantamab mafodotin	Added Embryo-fetal toxicity section and updated Impaired Male Fertility wording. Changes on Ocular Examination, Thrombocytopenia, Neutropenia, Infusion-Related Reactions, Hepatotoxicity, Potential Cardiotoxicity Related to Inflammatory Response, Nephrotoxicity, Pulmonary toxicity (pneumonitis), Immunosuppression, Potential for Other Laboratory Abnormalities.	Updated in accord with May 2019 FDA Guidance, Changes made based on results and experience from ongoing belantamab mafodotin clinical trials.
Section 8.3.7, SOAs Section 1.3, Section 17.2	Updated pregnancy wording follow-up timing and management of pregnancy.	Changes made based on results and experience from ongoing belantamab mafodotin clinical trials.
Section 5.1 Inclusion Criteria	Inclusion Criterion #9: updated contraceptive duration to 6 months for males and 9 months for females and requirement for men to use condoms even if they have undergone a successful vasectomy also added to inclusion criterion 9.	Updated in accord with May 2019 FDA Guidance and updated PK data
Section 1.3 SoA tables, and Section 8.3.1.	4. Updated timing of SAE assessments.	Updated timing of SAE assessments in line with program.
Section 16.1, Table 55	Toxicity Management and Dose Modification Guidance for IRRs wording updated.	Regulatory Agency request for updated data
Section 16.1, Section 16.1.2	A section added regarding Cytokine release syndrome (CRS),	Regulatory Agency request
Changes in Assessments and Schedules of Activities (SoAs)		
Section 1.3	SoA table for assessments done regardless of whether participant is dosed (SoA Table 4, Table 22, Table 32 and Table 43): removed physical	These evaluations are done with dosing

Section # and Name	Description of Change	Brief Rationale
	exam and vital sign assessment and updated footnote numbering.	
SOAs Section 1.3	Removed CRP assessment from SoA tables for Screening and SoA tables for assessments done regardless of whether a participant is dosed.	Changes made based on results and experience from ongoing belantamab mafodotin clinical trials.
Section 1.3	Clarification around timings for questionnaires, PK, biomarkers and bone marrow samples.	Clarifications
Section 1.3	Chemokines added where cytokines are collected as both cytokines and chemokines are being measured	Clarifications
Protocol Clarification and Alignment		
Section 1.1, Table 1 Dose Exploration, Table 2 Cohort Expansion Section 3, Objectives and Endpoints Table 8 Dose Exploration, Table 9 Cohort Expansion	An endpoint added for clarification to further evaluate the clinical measures of efficacy of GSK'916 (belantamab mafodotin) and combination treatments in each sub-study in participants with RRMM.	Clarification of efficacy evaluations.
Section 1.1, Overall design	Added wording around Sub-study closure. may be closed by Sponsor decision for reasons such as for lack of efficacy and/or undesirable toxicity	Clarity of wording around when a sub-study can be closed.
Section 1.1, Overall design, Section 4.1.2, Section 4.3	Added wording around the starting dose and monotherapy dose of belantamab mafodotin.	Clarification
Section 1.1 GSK Safety Review Team (SRT)	A study specific SRT will be implemented for this study comprised of the GSK study team. The SRT may also meet with investigators on a periodic basis.	Clarification of wording around the study specific SRT, who it comprises of and when they will meet.
Section 2.2.2	Role of B-Cell Maturation Antigen in Multiple Myeloma wording updated with new data	Regulatory Agency request for updated data
Section 4.1.1	Timing of interim analyses	Clarification of wording
Section 4.1.1, Section 9.2	New wording clarified as follows: However, the decision to move to the CE phase is based on the totality of the data	Clarification of wording
Section 4.4.2, Section 7.2	Definition of end of study and study withdrawal clarified	Regulatory Agency request for clarified wording
Section 5.2	Removal of exclusion criteria 22 as it was not deemed relevant for the study as anti PD1 inhibitors are not being studied.	Clarification
Section 5.3. Section 6.5.2	Live, live/attenuated vaccine wording	Clarification of timing, Regulatory Agency request.
Section 6.1, Table 14, Section 6.2	Infusion timing of GSK'916 (belantamab mafodotin added	Regulatory Agency request. Infusion timings added

Section # and Name	Description of Change	Brief Rationale
Section 6.6.3. Table 15, Table 16, Section 7.1	Clarification of wording around GSK'916 (belantamab mafodotin) dose delays, dose modification guidelines for belantamab mafodotin-related AEs, dose modification guidelines for belantamab mafodotin treatment-related eye disorders, discontinuation of study treatment	Clarification of wording
Section 8.8.2	Chemokines added where cytokines are collected as both cytokines and chemokines are being measured.	Clarification
Section 16.3	Section deleted and wording moved and amended with update information in Table 15 Section 6.6.	Clarification
Administrative Changes		
Section 17.1.8	Definition of source data added.	Regulatory Agency request
Section 17.1.9	Clarification of wording around study and site closure.	Regulatory Agency request
Editorial/Document Formatting Changes		
Throughout document	Minor editorial and document formatting revisions	Minor revisions therefore, have not been summarized

Amendment 1: 24 June 2019

Overall Rationale for the Amendment:

The protocol has been amended in line with comments from the US FDA, which include the following:

- 2 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory drug amended to at least 3 prior lines of therapy, including a PI, an immunomodulatory drug, and an anti-CD38 monoclonal antibody.
- More preclinical data included to provide the biological rationale for the use of GSK2857916 in combination with other anti-cancer treatments included in sub-studies 1 and 2.
- A lower starting dose for GSK2857916 and justification for the dose included.
- Lower starting doses for the combination partners in sub-studies 1 and 2 included.
- Dose-limiting toxicity (DLT) criteria revised.
- Modified toxicity probability interval (mTPI) design revised to include a targeted toxicity interval that is centered at ≤25%.
- Modified the hepatic function inclusion criteria to include participants with aspartate aminotransferase (AST) <2.5 × upper limit of normal (ULN).
- Modification of wording for potent inhibitor/inducer of major cytochrome P450 (CYP) enzymes
- Study stopping rules included for the Cohort Expansion (CE) phase.

Changes listed in the table below are for the Master protocol only. Changes for Protocol Amendment 1 that are related to specific sub-studies are tabulated at the beginning of each relevant sub-study section (Section 11 to Section 15).

Section # and Name	Description of Change	Brief Rationale
Revised Study Design		
Section 1.1 Synopsis	Updates to Safety Review Team and Data Review Committee sections	Additional details regarding safety monitoring and dose selection was added for clarity. A Data Review Committee (DRC) was added in addition to the GSK safety review team (SRT). The remit of the DRC is to support the SRT if requested during the conduct of DE and CE phases of the study, and to conduct a comprehensive risk:benefit analysis of all data at the conclusion of dose exploration and provide input into the selection of the RP2D.
Section 1.1 Overall Design and Number of participants Section 1.2 Schema Section 2.2.5.2.2 Clinical Activity Section 2.3.2 Benefit Assessment Section 4.1 Overall Design Section 4.1.3 Number of Participants Section 5 Study Population Section 5.1 Inclusion Criteria 3 Section 6.4 Measures to Minimize Bias: Randomization and Blinding- Section 9.2 Sample Size Determination	Participants to be enrolled changed from those who have been previously treated with at least 2 to those previously treated with at least 3 "prior lines that include the following: an immunomodulatory drug, proteasome inhibitor (PI) and anti-CD38 treatment (eg, daratumumab)". Added response data for participants receiving belantamab mafodotin who were refractory to both immunomodulators and proteasome inhibitors with prior daratumumab treatment. The number of participants per sub-study combination treatment to be enrolled in the DE and CE phases was changed from "approximately 55" to "approximately 85". Removal of prior anti-CD38	The number of prior lines of therapy was changed from 2 to 3 per FDA request to revise to a later line of therapy and supporting data added. Response data changed due to a hypothesis change from a 3rd line population where we target 60% response rate to a 4th line population where we target 40% response rate in monotherapy. Change in the number of participants per sub-study from 55 to 85 as requested by the FDA.
Section 1.1 Synopsis-The DE Phase	Number of responders needed at the end of the DE Phase to move forward into the CE Phase of each sub-study was changed from 4 to 2.	Changed due to a hypothesis change from moving from 3rrd line to 4th line.

Section # and Name	Description of Change	Brief Rationale
Section 4.1.1 Dose Exploration Phase Section 9.2 Sample Size Determination Section 9.5.1 Dose Exploration Phase Section 9.6.1 Impact of the timing when new sub-study starts-Table 17		
Section 1.1 Overall Design Section 4.1.1 Dose Exploration Phase Section 4.3 Justification for Maximum Starting Dose of belantamab mafodotin	Changes regarding the starting dose of belantamab mafodotin The starting dose of belantamab mafodotin in the DE phase was changed to 1.9 mg/kg from a maximum of 2.5 mg/kg. Added: "The justification for selecting the 1.9 mg/kg Q3W is as follow: 1) The 1.9 mg/kg Q3W dose is one dose level lower than the current lower dose of 2.5 mg/kg being evaluated, along with the 3.4 mg/kg dose, as monotherapy in the on-going pivotal phase 2 trial (Study 205678) in participants with RRMM. 2) Following administration of 1.9 mg/kg Q3W in the FTIH monotherapy study (BMA117159), target engagement was greater than 90% at the end of the first infusion based on decrease in plasma free sBCMA from baseline. 3) Based on the Bayesian logistic regression modelling of efficacy data in the FTIH monotherapy study (BMA117159 – 26 July 2017 cut-off), the 1.9 mg/kg Q3W dose has a response that is lower than at 2.5 mg/kg (predicted response rate 25.3% with a 95% credible interval of 9.4% and 42.2%); therefore, a dose lower than 1.9 mg/kg Q3W is considered not suitable as a starting dose."	As requested by the FDA to include a lower starting dose
Section 4.1 Overall Design Section 9.5.1 Dose Exploration Phase	Change from "three post-baseline assessments" to "3 efficacy assessments (1 baseline and 2 post-baseline assessments)"	Clarification of wording
Section 5.2 Exclusion Criteria 13	Additional Exclusion Criteria added: 13. Participants who have received prior therapy with belantamab mafodotin.	Clarification of wording
Section 6.5.2 Prohibited Concomitant Medications and Non-Drug Therapies	Clarification of wording regarding the use of belantamab mafodotin combined with strong inhibitors of Pgp and strong inhibitors of OATP.	As requested by the FDA
Section 6.6.2 belantamab mafodotin	Deleted text: "Intra-participant dose adjustment to the RP2D after DE"	Clarification of wording

Section # and Name	Description of Change	Brief Rationale
Dose Modification in DE		
Section 8.7.4 New Section 8.7 Immunogenicity Assessments	Original Section 8.7.4 deleted. New Section 8.7 created with updated text on immunogenicity assessments.	Description of immunogenicity assessments moved from Section 8.7.4 to Section 8.7 and updated
Safety Changes		
Section 2.3.1 Table 7 Risk Assessment for belantamab mafodotin	Changes were made to the following Potential Risk sections of Table 7: **Corneal Events:** Text describing data on corneal events from BMA117159 and the mitigation strategy was updated. **Thrombocytopenia / Neutropenia:** Separate "Thrombocytopenia" and "Neutropenia" sections were combined and text describing previous clinical data and the mitigation strategy was updated. **Infusion Related Reactions (IRRs):** Text describing the rationale for risk, data on IRRs from BMA117159, and the mitigation strategy was updated. **Hepatotoxicity:** Text describing previous non-clinical and clinical hepatotoxicity safety data was updated. **Potential Cardiotoxicity Related to Inflammatory Response:** Text describing previous non-clinical and clinical safety data was updated. **Nephrotoxicity:** Text describing previous nonclinical and clinical nephrotoxicity safety data was updated. **Pulmonary toxicity (pneumonitis):** Text describing previous nonclinical and clinical pulmonary toxicity data was updated. **Immunosuppression:** Text describing previous nonclinical data and the mitigation strategy was updated. **Potential for Other Laboratory Abnormalities:** Text describing other nonclinical and clinical laboratory abnormality data and the mitigation strategy was updated.	Updated to align with program level safety updates
Section 4.1.1.1 Dose-Limiting-Toxicity	DLT criteria for dose escalation revised to the following: **Hematologic:** Grade 3, 4 and 5 febrile neutropenia of any duration (ANC <1000/mm3 with a single temperature of >38.3°C [101°F], or a sustained temperature of 38°C [100.4°F] for more than one hour as per NCI-CTCAE V5.0) Grade 3, 4 and 5 thrombocytopenia accompanied by clinically significant bleeding. **Non-hematologic except corneal toxicity:** Grade 3, 4 and 5 toxicity Exceptions:	As requested by the FDA

Section # and Name	Description of Change	Brief Rationale
	Grade 3 or 4 nausea, vomiting, or diarrhea that can be controlled using symptomatic treatment Grade 3 hypertension (controlled following addition of up to 2 antihypertensive medications) Events and abnormalities which are unequivocally related to progression of underlying disease or comorbidities. Grade 3 or 4 tumor lysis syndrome (TLS), successfully managed clinically and resolves within 7 days without end-organ damage. **Corneal toxicity (using the GSK corneal grading scale):** Grade 4 per the GSK corneal grading scale (Section 16) **Other organ specific toxicities:** Liver toxicity, or other organ toxicity meeting prespecified GSK stopping criteria.	
Section 5.1 Inclusion Criteria	Inclusion Criteria #7, Table 13: Adequate organ Function AST <2.5xULN was added to the table.	As requested by the FDA
Section 7.1.3 QTc Interval Stopping Criteria	QTc wording modified to specify triplicate ECGs	Clarification of wording
8.2.7 Ophthalmic Examinations and Procedures	Information regarding follow-up ophthalmic exams was added.	Program level safety update
Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Text added to clarify AE and SAE timings: "SAEs will be assessed up to 90 days post last dose, or 45 days post last dose if the participant initiates a new anticancer therapy (whichever is shorter)"	Clarification of timings to agree with protocol text.
Section 16.3 Other Guidance for Toxicity Management and Dose Modification	Table 42 Other Guidance for Toxicity Management and Dose Modification Definition of febrile neutropenia was updated and guidance text for dose modification was updated. Guidance text for afebrile neutropenia was added.	Program level wording for febrile neutropenia, and afebrile neutropenia was revised.
Statistical Changes		
Section 4.1.1.2 mTPI in Dose Exploration Table 11	Design assumptions (target true underlying toxicity rate) and associated table were updated.	As requested by the FDA
Section 9.2.1 Statistical Operating Characteristics	The statistical operating characteristics and associated table were updated.	As requested by the FDA
Changes in Assessments and Schedules of Assessments (SoAs)		
Section 1.3 Table 3	• Clarified timings • Added Screening thyroid function tests	Clarification of wording and timings, and addition of missing tests
Section 1.3 Table 4	• Clarified timings/wording • Clarified AE/SAE timings to agree with text in the protocol: "AEs will be assessed up to 45 days post the last dose. SAEs will be assessed up to 90 days post last dose, or 45 days post last dose if the participant initiates a new anticancer therapy	Clarification of wording and timings, and removal of tests

Section # and Name	Description of Change	Brief Rationale
	(whichever is shorter). All related SAEs are to be collected from first dose through OS follow-up" • Spot urine (albumin/creatinine ratio) removed	
Section 1.3 Table 5	• Clarified timings/wording of PK, ADA, sBCMA samples • Day 4 Cycle 1 column added for clarity • "Ocular Examination" removed (to avoid confusion, this is carried out every 3 weeks regardless of dosing). • Clinical Chemistry: "with corrected calcium, corrected for albumin" removed • Added Thyroid Function Tests • ECOG performance status added • Deleted reference to EDTA tube & PAXgene tube	Clarification of wording and timings, removal/addition of tests and other edits for consistency between the SoA tables
Protocol Clarification and Alignment		
Appendix 2: Clinical Laboratory Tests	Table 43: Protocol-Required Safety Laboratory Assessments Modified list of tests and clarified the timing of lab tests to agree with the SoAs.	Modifications made for consistency with SoA tables.
Section 8.2.7.2 Ocular Examinations and Procedures	Modified wording.	Modifications in line with updated program level wording
Administrative Changes		
Appendix 11 Response Criteria (iMWG)	Removed Appendix 11 and deleted Table 50 Response Criteria (iMWG) and replaced cross reference with "Kumar, 2016".	The latest reference has been added to replace Table 50 to avoid outdated information in the protocol when changes are made to the response criteria.
Whole document	Changed the name of GS2857916 and GSK'916 (aBCMA) to belantamab mafodotin or GSK'916 for laboratory samples.	GS2857916 has a generic name.
Whole document	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

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